NCDEU

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Large Clinical Trials and Evidence-Based Practice

ABSTRACTS:
ORAL AND POSTER PRESENTATIONS

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NATIONAL INSTITUTES OF HEALTH

NIMH
National Institute
of Mental Health

ASCP
*American Society of
Clinical Psychopharmacology*

Oral Presentations*

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*Sources of funding for Oral Presenters are included with your conference materials.

NCDEU

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part I (9:00 a.m. - 12:00 p.m.)

Workshop Overview

Mark H. Rapaport, M.D.
Cedars-Sinai Medical Center

In this time of increased public scrutiny with stringent regulatory and congressional oversight and diminishing resources, it has become imperative to carefully assess and rigorously re-evaluate how we conceptualize treatment outcomes that are employed to determine the success of our experimental interventions. We need to stimulate the development of new types of instruments and assessment criteria as well as the use of new technologies to more precisely determine the efficacy of our interventions.

As Dr. Zerhouni indicated in his *Sounding Board*, "Translational and Clinical Science: Time for a New Vision" (NEJM, Oct. 13, 2005), we need to enhance interactions across disciplines to take advantage of rapidly evolving technologies and speed the development of novel treatment interventions. The goal of this full-day workshop is to critically evaluate how we think about acute and longer-term outcomes for individuals with mood and anxiety disorders, to discuss novel approaches to the design of instruments to measure these outcomes, and to determine how we can design studies to discern the presence or absence of treatment success while minimizing risks to human subjects.

This year's workshop will address core issues of recruitment, study design, measurements and endpoints to improve the quality and efficiency of clinical trials.

Learning Objectives:
• Rigorously re-evaluating the strength and weaknesses of our current definitions of adequate clinical response and remission to encompass more precise and less arbitrary standards.
• Examining current methodologies to assess response and present data-driven alternative approaches.
• Presenting new trial design alternatives that may decrease risk to subjects and speed completion of studies.
• Engage leaders in the field from academia, NIMH, Industry, and the FDA in a discussion of the merits of these initiatives.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part I (9:00 a.m. - 12:00 p.m.)

Pros and Cons of Study Designs Aimed at Minimizing the Placebo Response in Clinical Trials for Psychiatric Disorders

Maurizio Fava, M.D.
Massachusetts General Hospital

The placebo response is a major issue in clinical trials for psychiatric disorders. Over the past few decades, researchers have attempted to minimize the placebo effect in a variety of ways, typically with minimal or no success. More recently, specific study designs with the explicit goal of reducing the degree of placebo response have been developed, such as variable durations of placebo lead-in periods, prospective lead-in periods with active treatment (pharmacotherapy or cognitive-behavioral therapy), randomized discontinuation designs, and sequential parallel comparison designs. Empirical testing of all these various approaches needs to be carried out in a systematic fashion to inform investigators of their relative usefulness. This presentation will review the advantages and disadvantages of each of these approaches, followed by a discussion of issues that may emerge in their implementation in clinical trials.

Learning Objectives:
• Understand the most common study designs aimed at minimizing placebo response in psychiatric clinical trials.
• Understand the advantages and disadvantages of these designs.
• Appreciate the practical issues in implementing such design approaches to reduce the placebo response.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part I (9:00 a.m. - 12:00 p.m.)

The Role of Patient Reported Outcomes in the Understanding of Residual or "Leftover" Symptoms in Depressive Disorders

Georges M. Gharabawi, M.D.
Janssen Pharmaceutica, Inc.

Residual symptoms are frequently reported in patients with depressive disorders, including those who meet remission criteria. They are associated with lifetime-increased use of medical and psychiatric services, as well as social and functional impairment. However, there are limited research instruments available to identify residual symptoms, and to evaluate how troublesome they are to patients and their impact on quality of life and functioning.

The Most Troubling Residual Symptoms in Depression (MoTReS-D) is a patient-rated assessment created to identify and evaluate residual symptoms in depressive disorders. Patients are provided with a MADRS-derived list of core symptoms of depression and asked to rank their symptoms from the most to the least troubling. The severity of each symptom is then rated on a scale of 0-10 (0 = absent and 10 = extremely severe). Data demonstrated a high correlation between this bi-dimensional tool and other patient- and clinician-reported outcomes. Strengths and limitations of this approach will be discussed.

Learning Objectives:
• Understanding the impact of residual symptoms on functioning and quality of life in depression.
• Sharing the different attempts to identify and target residual symptoms.
• Sharing details about an innovative approach to evaluate residual symptoms in depression.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part I (9:00 a.m. - 12:00 p.m.)

Attrition in Psychopharmacology Trials

Andrew C. Leon, Ph.D.
Weill Medical College of Cornell University

Attrition is a critical problem in randomized controlled clinical trials of psychotropic agents. The consequences of attrition include biased estimates of the treatment effect, reduced statistical power, and restricted generalizability. Rates of attrition in RCTs for several DSM-IV disorders will be presented. Strategies for analysis of incomplete data will be compared. The convention of using last observation carried forward to account for attrition is strongly discouraged because its assumptions are typically inappropriate, whereas multiple imputation strategies are more appropriate. Mixed-effects models provide a useful strategy for incomplete data. In some cases, the inclusion of the propensity or pattern-mixture adjustments in mixed-models is beneficial. Finally, investigators are encouraged to include one additional Likert item to the weekly assessment package, "What is the likelihood that you will attend the next assessment session?" This inexpensive information can be used to eliminate some of the very obstacles that lead to attrition. We show that it can also be incorporated in data analyses to reduce, but not eliminate, attrition bias.

Learning Objectives:
• To understand the range of rates of attrition in psychopharmacology trials.
• To understand adverse consequences of attrition in psychopharmacology trials.
• To understand appropriate methods of accounting for attrition in psychopharmacology trials.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part I (9:00 a.m. - 12:00 p.m.)

Getting Serious: Seizures, Suicide, and Other Mortality in Depression, Anxiety, and Schizophrenia

Arif Khan, M.D.
Northwest Clinical Research Center

Background: Rare serious adverse events such as onset of seizures, suicide, suicide attempts, or mortality are a major concern when evaluating drug safety. The FDA generates a Summary Basis of Approval (SBA) dossier on each New Drug Application which details safety data on serious adverse advents.

Methods: We reviewed the SBA reports for thirteen antidepressants, six antipsychotics, and three anxiolytics in order to assess seizure, suicide, and mortality risk among 110,960 psychiatric patients participating in phase II and phase III clinical trials. We conducted chi-square analysis to evaluate differences in risk rates based on gross numbers as well as person exposure years (PEY) data for patients assigned to either a psychotropic or placebo.

Results: The seizure risk was ten times greater among patients with a psychiatric disorder compared to community non-patient samples. Some psychotropics (clozapine, clomipramine, bupropion IR, and alprazolam) appear to significantly increase seizure risk, whereas newer antidepressants (SSRIs and SNRIs) appear to significantly decrease seizure risk.

We did not detect any significant difference in suicide risk (suicide attempts and completed suicides) between depressed patients assigned to an antidepressant and those assigned to placebo. An analysis of three different databases indicated a ten-fold variability in suicide risk among the various antidepressant studies. A similar pattern emerged among two different databases for patients with schizophrenia.

PEY analysis for mortality rates among patients with schizophrenia indicated a significantly lower mortality rate among patients treated with an antipsychotic (atypical and typical) compared to patients assigned to placebo. Although not at significant level, the mortality rate was lower in patients assigned to an antidepressant compared to patients assigned to placebo. Conversely, patients treated with an anxiolytic had statistically higher mortality rates than those assigned to placebo. This finding was exclusively due to zero reported deaths for patients assigned to placebo.

Conclusions: These findings suggest that monitoring and interpreting serious, but rare adverse events is difficult and complicated. Interestingly, psychiatric diagnosis appears to play a significant role in the frequency as well as outcomes of these adverse events and possible effects of psychotropics. Some psychotropics with specific indications may have a deleterious effect, whereas other psychotropics may have beneficial effects. Other psychotropics appear to have no detectable effects. Thus, evaluations need to include appropriate drug indications, adequate sample sizes, and specific techniques for data analysis.

Learning Objectives:
• Appreciate the methods to analyze rare side effects associated with psychiatric medications.
• Understand differences in assessing both positive and negative rarely seen effects with psychiatric medications.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part II (1:00 p.m. - 4:00 p.m.)

Challenges for Global Rater Standardization

Steven D. Targum, M.D.
Massachusetts General Hospital and United Biosource Corporation

The competency of raters and the validity of rating instruments are often cited as prime factors in the failure to detect signal in CNS clinical trials. In fact, raters and rating instruments are only part of a much larger, interacting array of factors that influence signal detection. Within this context, attempts to conduct successful global studies using trial sites throughout the world have been confronted with numerous challenges that include diverse patient populations, cultural biases, diagnostic beliefs, as well as clinical experience. Training and qualification of raters to optimize scoring accuracy and assessment of their interviewing skills is harder when multiple languages and learning styles are involved. Existing CNS rating instruments often compound the problem. This presentation will offer case studies of rater-rating instrument issues that may affect signal detection in CNS studies.

Learning Objectives:
• Understand frequently encountered issues confronting multi-national clinical trials.
• Appreciate the broad range of clinical and ratings experience that raters bring to clinical trials.
• Appreciate the cultural issues that may affect scoring patterns on typically used CNS rating instruments.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part II (1:00 p.m. - 4:00 p.m.)

With Apologies to Max: New Definitions of Depression Intervention Endpoints

Ellen Frank, Ph.D.
University of Pittsburgh School of Medicine

I knew Max Hamilton. I even had the privilege of training with him on his now iconographic instrument and hearing him talk about what he had in mind when he developed it. And it had nothing to do with how we are using it today. The Hamilton Rating Scale for Depression was developed for the measurement of the relative severity of depression among hospitalized patients, most of whom had melancholia. It was never intended as a measure of change. And it certainly was not intended to assess change in mildly to moderately depressed outpatients. But because it became the industry (both the pharmaceutical industry and the academic research industry) standard, linking new research to old, we have been remarkably reluctant to give it up.

Finally, a convergence of forces is calling on us to develop new endpoints for studies of depression. Those forces include academic and pharmaceutical industry investigators who recognize the need for more sensitive measures and for measures that cover more forms of depressive illness (including bipolar depression, minor depression, and dysthymia), services researchers who are seeking assessment measures that fit more naturally with community intervention, and, perhaps most important, patients who not surprisingly tell us that what the HRS-D measures is not necessarily what they care about...or not what they care about at all. What patients and patient advocacy groups tell us they want out of treatment are a home, meaningful relationships, and satisfying work.

This presentation will be aimed at stimulating discussion about how best to satisfy these three groups of stakeholders in the depression endpoint measurement enterprise. The key questions will include 1) whether we should be aiming for a single broad measure or multiple measures for different forms of depression, 2) what the best methodologies are for obtaining assessments in a world with ever more sophisticated technology, and 3) how best to represent the goals of the most important stakeholders in the intervention enterprise – our patients – in the development of new depression endpoints.

Learning Objectives:
• Should we be aiming for a single broad measure or multiple measures for different forms of depression?
• What are the best methodologies for obtaining assessments in a world with ever more sophisticated technology?

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part II (1:00 p.m. - 4:00 p.m.)

The End of the Beginning: New Definitions of Anxiety Disorder Endpoints

Michael R. Liebowitz, M.D.
New York State Psychiatric Institute

There are a number of ways to increase the reliability, validity, and utility of our outcome criteria in the anxiety disorders. Recent developments in panic disorder and social anxiety disorder will be used as examples.

In panic disorder, a recent paper by Rapaport et al highlighted the fact that sertraline and placebo responders defined by symptom criteria differed in terms of functioning-quality of life, suggesting that relying on symptom criteria alone might blur some of the difference between drug and placebo. Another trial, reported by Barlow et al, revealed that responder status defined by percentage of symptom improvement was better at separating drug from placebo than was responder status defined by global improvement. A third study (Liebowitz et al, in preparation) demonstrates that using attainment of zero panic attacks per week is a less sensitive outcome than relying on ratings that also include behavioral features such as phobic avoidance.

Several developments in rating social anxiety illustrate ways to utilize the information and/or overcome the problems described above. In an early step, the Liebowitz Social Anxiety Scale (LSAS), which has become a frequently used primary outcome measure, was designed to rate both anxiety and avoidance, to avoid the dilemma of whether to rely on symptom or behavioral outcomes that has troubled the panic disorder field. More recently, a newly developed digital data capture (DDC) approach permits the programming of corresponding ranges among different measures. As a result, for example, a global rating that is out of line with symptom measures for a given patient is brought to the attention of a rater in real time, permitting revision if the rater considers this appropriate. Similarly, responder status judgments that are based on global or symptom measures can also be informed by functional status, giving the rater a more informed view of a subject's condition. The DDC also leaves an audit trail, so that raters who generate frequent significant inconsistencies among measures can be identified, and if desired, remediated with further training during the course of a trial.

Learning Objectives:
• To become informed about some of the recent findings concerning outcome measues in panic disorder trials.
• To become informed about approaches taken to rating social anxiety that attempt to integrate the findings and overcome the problems found in rating panic disorder.
• To become informed about innovations in digital data capture that are adding to the validity, reliability, and utility of ratings in social anxiety trials.
• To consider the application of the new rating approaches to panic and other anxiety disorders, and to other psychiatric disorders.

WORKSHOP 1

Enhancing Precision in Clinical Trials IX: Recruitment, Study Design, Measurement, Endpoints
Part II (1:00 p.m. - 4:00 p.m.)

Ascertainment of Rare and Classically Drug-Related Adverse Events

Paul J. Andreason, M.D.
Food and Drug Administration

Acute liver failure and Stevens-Johnson syndrome (SJS) are very rare events. When they occur in association with the use of a new drug, the drug is often suspected. When one of these events is reported in the context of a clinical development program, then it is vital to follow its course closely. A recent Psychiatric Drug Advisory Committee recommended against approving modafinil for the treatment of ADHD based on a report of Stevens-Johnson syndrome in one child. Photographs and a biopsy were not available, and experts had to rely on history alone to make a case assessment. When SJS is reported, it is vital to collect photographs and a biopsy. Likewise, adverse event reports of serious liver injury or potentially clinically significantly increased transaminase values must include not only transaminase values, but bilirubin, concomitant drugs used over time, and an alcohol intake history.

Learning Objectives:
• Acute liver failure and Stevens-Johnson syndrome occur rarely.
• Even single cases of SJS or acute liver failure impact drug development.

WORKSHOP 2

Bridging the Gap: Developing Minority Mental Health Researchers
9:00 a.m. - 10:30 a.m.

Workshop Overview

Jacobo Mintzer, M.D.
Medical University of South Carolina

Enid Light, Ph.D.
National Institute of Mental Health

Objective: To identify successful strategies to develop independent mental health minority researchers.

Background: During the last two decades the National Institute of Mental Health and the National Institute on Aging have identified the development of independent minority researchers in the area of mental health as an important goal. The relevance of achieving this goal can be justified from the perspective of multiple domains. It is believed, however, that researchers from diverse backgrounds will bring a unique and important perspective to the field that will enrich our understanding of mental disorders irrespective of the specific area on which these researchers choose to focus. The process to achieve this goal has been difficult, and success has required the use of diverse and innovative approaches.

Methods: This workshop brings together the directors of three diverse, yet successful programs that aim to develop independent minority mental health researchers. The three directors will briefly introduce their programs and present the unique approaches used to recruit, retain, and successfully train minority researchers in mental health. They will also present the successes and failures of the programs as well as their trainees. The presentation will be followed by two discussants who will evaluate the presentations and provide their own perspective of the issues.

Results: Evaluation of the programs demonstrates the three programs to be successful in placing program graduates in academic or public institutions. All three programs have identified the availability of a committed mentor to be an essential factor for success. Large proportions of the graduates are independently funded or hold research positions. Two of the programs report that Ph.D. students have a smoother transition to the research development program as opposed to their M.D. counterparts. Further differences and similarities of the programs will be discussed, including the importance of addressing social and environmental issues.

Conclusion: Minority-focused research development programs report positive outcomes in the recruitment and retention of minority researchers. The presence of some common key elements appears to be of relevance.

Learning Objectives:
• Participants will be able to identify successful strategies to develop independent mental health minority researchers.
• Participants will be able to identify barriers that limit the development of mental health minority researchers.
• Participants will be able to identify common features in available minority research training programs that have been associated with successful outcomes.

WORKSHOP 2

Bridging the Gap: Developing Minority Mental Health Researchers
9:00 a.m. - 10:30 a.m.

The Program for Minority Research Training in Psychiatry: Where Have We Been, Where Are We Going?

Darrel A. Regier, M.D., M.P.H.
American Psychiatric Institute for Research and Education

Initiated in 1989 in response to the need to train more minority physicians as mental health clinical researchers, the American Psychiatric Association's (APA) Program for Minority Research Training in Psychiatry (PMRTP) has been designed to overcome the barriers to research careers among underrepresented minority medical students and psychiatric residents. This presentation will review the history, scope, structure, and outcomes of the program. In addition, the incorporation of new technologies for a "second generation" PMRTP, stimulated by the internet and the development of long-distance training initiatives, will be discussed.

Learning Objectives:
- Participants will be able to identify major elements of the PMRTP, understand its approach to the training of minority psychiatric researchers, and assess its outcomes.
- Participants will develop an understanding of issues related to the recruitment, development, and training of minority psychiatric clinical researchers, from the perspective of PMRTP.

WORKSHOP 2

Bridging the Gap: Developing Minority Mental Health Researchers
9:00 a.m. - 10:30 a.m.

Lessons from Institute for Research Minority Training on Mental Health and Aging

Jacobo Mintzer, M.D.
Medical University of South Carolina and Ralph H. Johnson Veterans' Affairs Medical Center

IRMMA is the Institute of Research Minority Training on Mental Health and Aging. This program provides post-doctoral training for three promising minority investigators a year interested in mental health and aging. The program offers a masters in research methodology and biostatistics, in addition to salary support and coaching for a K-type award submission at the end of the 3-year program. Although successful in recruitment and outcomes, the program has confronted unexpected cultural challenges. Fellows had to be guided through the unwritten rules of the scientific world. Often, those rules collated with long-held community expectations and roles. We were surprised to learn that grant writing and learning were the smallest of the obstacles our fellows had to confront. These issues will be discussed at length during the presentation.

Learning Objectives:
• Participants will become familiar with the cultural obstacles minority scientists confront.
• Participants will become familiar with mentoring strategies to aid minority researchers to achieve their career goals.
• Participants will become aware of available resources to help minority researchers succeed in their careers.

WORKSHOP 2

Bridging the Gap: Developing Minority Mental Health Researchers
9:00 a.m. - 10:30 a.m.

Public-Private Partnerships: Innovations and Other American Anachronisms

Rick A. Martinez, M.D.
Johnson & Johnson

Partnerships in the field of biomedicine between public institutions of higher learning and industries in the private sector are topics of considerable media attention. There are many types of partnerships between these institutions. Many, if not most, achieve mutual benefit that promotes successful outcomes, such as career development for junior-level investigators to formal research and technology transfer. Yet the trend in editorials that characterize these relations in terms of conflicts of interest are forcing an important public debate about the nature of these interactions. In this panel, presenters from an academic institution and a pharmaceutical and device company will review the motivation for a partnership/sponsorship of one type of relationship to highlight the importance for a coherent legal/regulatory environment necessary for progress in the field and its future human resource needs.

Learning Objectives:
• Stimulate a discussion on the direction of public-private relationships taken in the current environment.
• Evaluate the controversy regarding private support of academic career development.
• Learn what a successful public-private partnership looks like.

WORKSHOP 3

New Uses for Old Technologies: Telepsychiatry and Biomarkers in Psychiatric Clinical Drug Trials
9:00 a.m. - 12:00 p.m.

Workshop Overview

John M. Kane, M.D.
The Zucker Hillside Hospital and Albert Einstein College of Medicine

The challenges associated with testing the effectiveness of new treatments in psychiatry have prompted evaluation of new approaches and methodologies that may positively impact the ability to discriminate drug and placebo treatment. Telepsychiatry and biomarker research are two examples of existing research tools that are being put to new uses in psychiatric clinical drug trials. The workshop will focus on the past and present strengths and limitations of these modalities, as well as on their broader implications, from study design, analytic, ethical, and regulatory perspectives.

Telepsychiatry, in the form of videoconferencing and other modalities, is subsumed under the broader area of telemedicine, and has been used successfully for a variety of clinical services and educational initiatives. Once criticized for being overly complex, impractical, and of little value in research settings, within the field of clinical trials, telepsychiatry is emerging as a viable alternative to in-person assessments, with particular advantage demonstrated in obtaining standardized, reliable assessments at fewer sites and with fewer raters.

The desire for biomarkers in psychiatric diseases has produced many promises, but has yet to become a mainstream component of clinical research. Some recent successes, reviewed in this workshop, have moved beyond the exploratory phases of development to the point where they hold promise as either primary or secondary endpoints. The integration of biomarkers with valid measures of symptom severity may herald a new model for future clinical trials.

Speakers in this workshop will provide both current and historical perspectives on telepsychiatry and biomarker research and present recent findings demonstrating the application of these tools in clinical research. A panel comprising representatives from the Food and Drug Administration and the field of bioethics will discuss the regulatory and ethical aspects of using these methodologies to assess outcome in clinical trials and practice.

Learning Objectives:
• Participants will learn the strengths and limitations of new applications of telepsychiatry and biomarkers in assessing treatment outcome in psychiatric clinical trials.
• Participants will understand the ethical and regulatory implications of using these applications to evaluate outcome in clinical drug trials.

WORKSHOP 3

New Uses for Old Technologies: Telepsychiatry and Biomarkers in Psychiatric Clinical Drug Trials
9:00 a.m. - 12:00 p.m.

Innovations in Telepsychiatric Research: Outcomes, Satisfaction, Models of Service Delivery, and Recruitment of "New" Subjects

Don M. Hilty, M.D.
University of California, Davis

E-health in the form of videoconferencing, telephone, and secure email has matured and is increasingly used in clinical care, education, and research. Videoconferencing for psychiatric care (telepsychiatry) is well-received by participants, is affordable, and is versatile. Outcomes are increasingly studied through clinical trials. This presentation will briefly review historical developments in the use of telepsychiatry for research. It will also present data on satisfaction and clinical outcomes, in ethnic populations as available. Finally, it will discuss models of service delivery and how outreach to rural areas is a novel way to recruit "new" subjects.

Learning Objectives:
• To learn how telepsychiatry has come of age and facilitates clinical research.
• To learn outcomes for studies involving telepsychiatry.

WORKSHOP 3

New Uses for Old Technologies: Telepsychiatry and Biomarkers in Psychiatric Clinical Drug Trials
9:00 a.m. - 12:00 p.m.

Use of Telepsychiatry in Psychiatric Clinical Trials

Nina Engelhardt, Ph.D.
MedAvante, Inc.

Telepsychiatry, or the use of various information and electronic communication technologies to support psychiatric care, education, and research, holds particular promise as a tool for conducting psychiatric assessments in clinical trials as well as evaluating and training personnel to conduct reliable psychiatric assessments. This session will explore the application of telepsychiatry to the training and administration of psychiatric rating scales in clinical trials. Use of new technologies for training raters and assessing patients using two-way audio and videoconferencing will be presented. The use of videoconferencing to remotely assess patients from a centralized location in real-time is currently being employed in multi-center schizophrenia and depression trials. Data supporting the rationale for the use of centralized remote raters will be presented and discussed.

Learning Objectives:
• Participants will understand the challenges associated with obtaining reliable efficacy ratings in psychiatric clinical research.
• Participants will evaluate the potential of telepsychiatry versus standard methods to enhance the reliability of psychiatric assessments in multi-center clinical drug trials.

WORKSHOP 3

New Uses for Old Technologies: Telepsychiatry and Biomarkers in Psychiatric Clinical Drug Trials
9:00 a.m. - 12:00 p.m.

The (Re) Birth of Biomarkers in Clinical Trials of Psychiatric Disorders

Mark G. Opler, Ph.D., M.P.H.
Columbia University and The PANSS Institute

Clinical studies of psychiatric disorders are complicated by the almost universal absence of reliable physical or biochemical pathologies. Over the last two decades, biological markers of many disorders, including depression, schizophrenia, and Alzheimer's disease, have fallen in and out of favor. However, biomarkers are making a comeback as increasing numbers of studies routinely collect biological material and employ "hybrid" measures that combine traditional approaches to data collection with tests of biochemical and systemic function. There is renewed interest in searching for biological markers that can be used to diagnose, subtype, or quantify disease severity. Among the types of biological markers categorized over two decades ago by Buchsbaum, Haier, and others, various candidates for etiologic and diagnostic markers, challenge markers, and linkage markers are being tested. A valuable new category is also beginning to emerge, as biomarkers to predict treatment response subtypes. This presentation will review the latest evidence in each type of marker, discuss various examples, and outline existing challenges.

Learning Objectives:
• Participants will review the principles of biomarker development and validation, using examples of past and recent attempts from psychiatric research to gauge the current state of the field.
• Participants will learn how new and old types of biomarkers may be applied to future trials, including the benefits and liabilities that may follow.

WORKSHOP 3

New Uses for Old Technologies: Telepsychiatry and Biomarkers in Psychiatric Clinical Drug Trials
9:00 a.m. - 12:00 p.m.

Neurophysiological Biomarkers as Endpoints in Clinical Trials of Schizophrenia

John A. Sweeney, Ph.D.
University of Illinois, Chicago

In clinical trials of procognitive medications, efficient and precise approaches are needed to characterize the beneficial and adverse effects of drugs on neurocognitive abilities. Eye-movement studies have provided a quantitative biomarker for studying cognitive and motor systems for decades. In animal models, they have provided a powerful tool for monitoring beneficial and adverse effects of CNS active drugs, especially on working memory systems. While studies of eye-tracking in psychiatry began with interest in their use as an endophenotype for family/genetic research, more recent work has shown that studies of eye movements hold great promise as a translational biomarker in testing the neurocognitive efficacy of treatments. In longitudinal studies of first episode schizophrenia, oculomotor and neuropsychological tests have been administered and compared across different disease and treatment conditions. In oculomotor studies, improvement in the ability to suppress context-inappropriate responses has been observed after treatment, but more gradually than the more rapid reduction in psychotic symptoms. While benefits are seen during treatment, treatment emergent adverse cognitive effects have been seen as well in the areas of spatial working memory and procedural learning, along with a modest decline in motor function. Neuropsychological test data, consistent with the literature, indicated more modest signs of improvement that were consistent across domains rather than differentiated. These findings provide evidence for the superior sensitivity of neurophysiological testing for detecting significant and specific changes in neurocognitive systems observed after pharmacological treatment relative to standard neuropsychological tests. Translational approaches to monitoring drug effects on brain systems may be particularly advantageous for early proof-of-concept and dose-ranging studies where translational modifications of animal model paradigms can be especially valuable.

Learning Objectives:
- Participants will learn to evaluate the potential for oculomotor and neurophysiological tests as endpoints in trials of CNS-active medications.
- Participants will understand the strengths and limitations of neurophysiological measures compared with standard tests of neuropsychological nction in treatment studies of cognitive deficits in schizophrenia.

WORKSHOP 4

Comparing ETRANK, MMRM, and LOCF Statistical Methods of Analysis
10:45 a.m. - 12:15 p.m.

Workshop Overview

A. Richard Entsuah, Ph.D.
Wyeth Research

The inevitability of patient attrition, and therefore missing data points, during longitudinal clinical trials complicates statistical analysis of these data and the interpretation of the results of these analyses. The Last Observation Carried Forward (LOCF) method, which traditionally has been used for the primary analysis in registration studies in the United States, uses the last recorded data point to replace the missing points for a participant failing to complete the trial. This approach is believed to be the most conservative because it could penalize patients by assigning high scores for medications that are not well tolerated; however, recent comparisons of different methods have demonstrated that that assumption might not be true in all cases. Mixed-model Repeated Measures (MMRM) analysis is one type of likelihood-based mixed-effects methods, in which missing points are estimated based on observed data. MMRM provides an alternative method for analyzing longitudinal data based on certain assumptions. ETRANK uses a nonparametric (randomization) technique to analyze incomplete repeated measures data when premature withdrawal is deemed to be non-random and related to treatment. In this method, all observed or endpoint data are used to create empirical significance levels from time point descriptive statistics. This session will compare the assumptions and limitations associated with common methods of statistical analysis that have been developed to compensate for missing data points, using an analysis of data from short-term depression studies to illustrate differences in the results obtained with each method.

Learning Objectives:
• Discuss how different reasons for missing data affect the results of statistical analysis.
• Describe relative utility of LOCF, MMRM, and ETRANK methods for analyzing data.

WORKSHOP 4

Comparing ETRANK, MMRM, and LOCF Statistical Methods
of Analysis
10:45 a.m. - 12:15 p.m.

Attrition and the Choice of Statistical Methods to Handle Missing Data

Michael E. Thase, M.D.
University of Pittsburgh School of Medicine

Although the randomized controlled trial (RCT) continues to be the "gold standard" for assessing the efficacy of psychotropic medications, a number of factors can compromise the "assay sensitivity" of this venerable method. In fact, dating to the early 1980s, approximately 50% of all RCTs of antidepressants with known efficacy have failed to detect statistically significant drug-placebo differences. A number of disparate factors appear to contribute to such declining assay sensitivity, including the heterogeneity of major depressive disorder, increasing expectation of significant drug benefits, inadvertent selection of more placebo-responsive subsets of patients, and suboptimal administration of standardized rating scales. This workshop will focus on yet another potential "contaminant" of the gold standard: attrition and the choice of statistical method to handle the data of study participants who do not complete RCTs. The Last Observation Carried Forward (LOCF) method is a conservative and easy-to-implement approach and has been the accepted regulatory standard for new drug applications for decades. There is increasing recognition, however, that the several strengths of this approach are outweighed by a number of serious limitations that negatively impact assay sensitivity. In this workshop, the limitations of the LOCF method will be illustrated and several alternate approaches for handling the data of patients who do not complete RCTs will be critically examined.

Learning Objectives:
• Become familiar with the effects of attrition on clinical trials.
• Become familiar with statistical methods to deal with missing data due to attrition.

WORKSHOP 4

Comparing ETRANK, MMRM, and LOCF Statistical Methods of Analysis
10:45 a.m. - 12:15 p.m.

Choice of the Primary Analysis in Longitudinal Clinical Trials: Focus on MMRM and LOCF

Craig H. Mallinckrodt, Ph.D.
Eli Lilly and Company

Missing data and the bias they can cause are an almost ever-present concern in clinical trials. The Last-Observation-Carried-Forward (LOCF) approach has been frequently utilized to handle missing data in clinical trials and is often specified in conjunction with Analysis of Variance (LOCF ANOVA) for the primary analysis. Considerable advances in statistical methodology and in our ability to implement these methods have been made in recent years. Likelihood-based Mixed-effects Model Repeated Measures (MMRM) approaches are now easy to implement, are commonly used to analyze clinical trial data, are more robust to the biases from missing data, and provide better control of type I and type II errors than LOCF ANOVA. This presentation will briefly review the theoretical basis for and research behind these findings. The clinical implications of the differences between MMRM and LOCF will be illustrated by comparing results from MMRM and LOCF on every a priori specified mean change analysis from every placebo controlled clinical trial included in a recent NDA. It is concluded that practice should shift away from using LOCF ANOVA as the primary analysis and greater focus should be placed on likelihood-based mixed-effects model approaches.

Learning Objectives:
• To discuss how missing data and the bias they can cause are an almost ever-present concern in clinical trials.
• To discuss that practice should shift away from LOCF ANOVA as the primary analysis and greater focus should be placed on likelihood-based mixed-effects model approaches.

WORKSHOP 4

Comparing ETRANK, MMRM, and LOCF Statistical Methods of Analysis
10:45 a.m. - 12:15 p.m.

Comparing the ETRANK, MMRM, and LOCF Analytic Methods in Clinical Trials with Missing Data

A. Richard Entsuah, Ph.D.
Wyeth Research

The challenges facing clinical trials due to patients dropping out during randomized controlled trials (RCT) prior to trial completion cannot be over-emphasized. This difficulty has led to the development of new statistical approaches to resolve some of these challenges. Statistical methods that have been developed to interpret data with missing values include ETRANK, MMRM (mixed model repeated measures), and LOCF (last observation carried forward).

A description of the ETRANK method will be provided at this workshop. Demonstration of this technique will be shown using venlafaxine clinical trial data. Application of ETRANK, MMRM, and LOCF statistical methods have been applied to 18 placebo-controlled venlafaxine clinical trials for the treatment of major depressive disorders. Analysis was conducted using the LOCF, MMRM, and ETRANK methods. The MMRM analysis was used to evaluate the main effect of treatment and interaction of treatment by time. Changes from baseline on the 17-item Hamilton Rating Scale for Depression (HAM-D$_{17}$) were used as the dependent variable. Remission of symptoms, defined as HAM-D$_{17}$ ≤ 7, also was analyzed using the LOCF_Logistic Regression and the Glimmix MMRM analyses. These analyses were performed on data from 18-placebo controlled trials of venlafaxine/venlafaxine extended release formulation.

The merits in the use of each of these statistical methods and their applications in randomized clinical trials with missing values will be discussed.

Learning Objectives:
• The merits in the use of each of these statistical methods and their applications in randomized clinical trials with missing values will be discussed.
• Demonstration of this technique will be shown using venlafaxine clinical trial data.

WORKSHOP 4

Comparing ETRANK, MMRM, and LOCF Statistical Methods of Analysis
10:45 a.m. - 12:15 p.m.

Looking Toward New Analyses Models in Depression and Anxiety Studies

David V. Sheehan, M.D., M.B.A.
University of South Florida College of Medicine

The Last-Observation-Carried-Forward (LOCF) model is very punitive, which does not accurately reflect reality. It is a worst case scenario model, and there are a number of consequences to restricting ourselves to such a model.

First, larger sample sizes are needed to detect statistical difference between drug and placebo with the LOCF model in depression and anxiety studies. As a result, more patients have to be exposed to the risk of investigational drugs before you get an answer to the research question at hand and before the drugs can be approved by the Food and Drug Administration. There are ethical concerns that will need to be addressed if more patients need to be exposed to risk. On the other hand, with the ETRANK analysis the research question can be addressed while fewer patients are exposed to risk, and the ETRANK analysis may reflect reality more accurately. In addition, there are cost consequences in drug development when using one statistical model compared with another. Because there are finite financial resources available to develop all drugs, it means that fewer drugs can be developed with the available resources at the available time using one model versus the other. This has both public health and ethical implications. Basic assumptions required by hierarchical linear analysis models, LOCF and MMRM, are not violated by the ETRANK analysis, which is a more robust and defensible model to use in anxiety and depression studies.

Learning Objectives:
• To inform participants of the advantages of the ETRANK analysis model.
• To engage participants in a discussion about ethical concerns of other analysis models.
• To discuss the future direction of these analysis models and what benefits they have for future drug investigations.

WORKSHOP 5

Adaptive Treatment Design: The Clinical Need, the Design, and Analytic Challenges
1:00 p.m. - 2:30 p.m.

Workshop Overview

A. John Rush, M.D.
University of Texas Southwestern Medical Center

Most psychiatric and substance abuse disorders are chronic or recurrent conditions that are heterogeneous with regard to response. Some treatments work for some patients, while different treatments are needed for others. Current practice often entails a trial and error approach to identify the best treatment for a specific patient. Most patients are subjected to a sequence of treatments or a package of treatment components, employed at various times depending upon response to the prior treatments or components. Adaptive treatment designs represent attempts to address these critical clinical issues often with a series of experiments, first to raise hypotheses, and then to test prospectively these initial findings. Study designers are confronted with a large range of questions that must be addressed in order to prioritize the clinical questions, select indicator variables, and define the preferred timeframes and outcomes of major interest. This panel will illustrate the development and application of adaptive treatment designs to disorders and treatments for psychiatric and substance abuse conditions. The panel will provide presentations and discussions of (1) the clinical need for innovative study designs and analytic approaches to better inform practitioners about the choice, timing, and duration of various potential treatments (Dr. Rush); (2) the use of a Sequential Multiple Assignment Randomized Trial (SMART) design as an example of adaptive treatment designs to identify preferred treatment sequences (strategies) (e.g., is A-B-C better than B-C-A) (Dr. Murphy); (3) adaptive designs that can inform us as to which treatment components should be introduced (when and for whom) in a multi-component substance abuse treatment program (Dr. Collins); and (4) additional adaptive designs and analytic approaches to inform clinicians about changes in treatment approaches (type, dose, timing) that would be informative for optimizing the long-term outcomes of mood or psychotic disorders (Dr. Oslin).

Learning Objectives:
• Participants will understand the clinical rationale for considering adaptive designs.
• Participants will become familiar with various adaptive treatment designs as applied to chronic or recurrent mental illness.

WORKSHOP 5

Adaptive Treatment Design: The Clinical Need, the Design, and Analytic Challenges
1:00 p.m. - 2:30 p.m.

The Clinical Need for Adaptive Designs

A. John Rush, M.D.
University of Texas Southwestern Medical Center

This presentation will highlight the need for adaptive clinical trial designs for studies of chronic or recurrent disorder for which no one treatment is a panacea, and for which biomarkers are not available by which to precisely match a particular treatment to a particular disorder (or subtype). The issue will be illustrated by way of case examples. Present practice entails a trial and error approach, beginning with a treatment that is to be delivered for an adequate duration. Sometime during the trial, a judgment is made that a change in the dose or type of treatment is needed. The precise timing of the decision is unknown. Thus, one can randomize the change at various time points to establish the optimal timing of the switch.

Following the initial treatment, subsequent treatment steps are employed. Again, the best second step can be inferred from randomized comparisons. But, a third treatment is often needed as well. It is possible that the best second step treatment is not part of the optimal path if subsequent treatments are also required. In addition, longer-term outcomes are critical in chronic conditions, and treatments are often added or subtracted over time. When such changes should be made, and what treatments are best, is unclear. Designs that help us to identify the best multi-step sequence of treatments for particular patients are called for. The subsequent presentation will illustrate such efforts.

Learning Objectives:
• Participants will understand why adaptive designs are needed for chronic/recurrent disorders.
• Participants will understand the limitations of designs that focus only on best outcomes at each treatment step.

WORKSHOP 5

Adaptive Treatment Design: The Clinical Need, the Design, and Analytic Challenges
1:00 p.m. - 2:30 p.m.

SMART Trials for Developing Adaptive Treatment Strategies

Susan A. Murphy, Ph.D.
University of Michigan

Adaptive treatment strategies are individually tailored sequences of treatments. The development of these treatment strategies requires consideration of the ordering of treatments and the timing of changes in treatment. Furthermore, measures such as patient response, side effect burden, and adherence may be used to tailor the treatment sequence to the patient. The Sequential Multiple Assignment Randomized Trial (SMART) is particularly useful in developing adaptive treatment strategies. Simple analyses that can be used with the SMART design will be described. Furthermore, we compare the SMART design with standard experimental designs.

Learning Objectives:
• What are adaptive treatment strategies?
• What kinds of randomized trial designs will help in formulating an adaptive treatment strategy?
• What kinds of analyses can be conducted using data from a SMART Trial?

WORKSHOP 5

Adaptive Treatment Design: The Clinical Need, the Design, and Analytic Challenges
1:00 p.m. - 2:30 p.m.

The Multiphase Optimization Strategy (MOST) for Building and Evaluating Adaptive Interventions

Linda M. Collins, Ph.D.
Pennsylvania State University

This talk will present the Multiphase Optimization Strategy, an extension of clinical trials methods aimed at building optimized multi-component behavioral interventions. MOST consists of the following three phases: (1) *screening*, in which randomized experimentation closely guided by theory is used to asses an array of program and/or delivery components and select the components that merit further investigation; (2) *refining*, in which interactions among the identified set of components and their interrelationships with covariates are investigated in detail, again via randomized experiments, and optimal dosage levels and combinations of components are identified; and (3) *confirming*, in which the resulting optimized intervention is evaluated by means of a standard randomized clinical trial. In order to make the best use of available resources, MOST relies on design and analysis tools that help maximize efficiency, such as fractional factorial analysis of variance. MOST has the potential to help increase the potency of adaptive interventions, by providing a principled way of investigating how potential tailoring variables may interact with treatment and how best to adjust dose in response to tailoring variables.

Learning Objectives:
• Learn about an expanded approach to clinical trials.
• Learn about research design alternatives.

WORKSHOP 5

Adaptive Treatment Design: The Clinical Need, the Design, and Analytic Challenges
1:00 p.m. - 2:30 p.m.

Enhancing Treatment Adherence for Alcohol Dependent Patients

David W. Oslin, M.D.
University of Pennsylvania

Objectives: Poor treatment adherence is known to be associated with unsuccessful clinical outcomes in pharmacotherapy studies. Poor adherence is also a feature of managing many chronic disorders such as alcohol dependence. Prior research in the addiction field has focused on enhancing the incorporation of adherence monitoring and strategies into the treatment model. The focus of our current work is on enhancing adherence by adapting or modifying treatment based on response to treatment at key times.

Method: One hundred forty-three alcohol dependent patients (104 from a SMART study and 39 from a randomized placebo controlled trial) who were assigned to naltrexone and a weekly psychosocial intervention focused on medication adherence were evaluated for adherence to treatment during the first 8 weeks of participation. In addition to the naltrexone and supportive therapy, those in the adaptive study were monitored for alcohol use during the 8 weeks and offered the addition of a cognitive behavioral intervention if they began to relapse.

Results: Participants in the two trials had similar pretreatment severity of drinking and were comparable on demographic factors. Participants in both trials also had similar rates of relapse. In the study using a fixed treatment, 51% of the patients completed 8 weeks of treatment. In contrast to the fixed treatment trial, a total of 70% of the participants in this trial completed 8 weeks of treatment. Moreover, 56% of the patients in the adaptive treatment who relapsed and were offered additional therapy completed 8 weeks of treatment.

Discussion/Significance: These observations suggest that the adaptations during treatment may be an important way to improve adherence to treatment that may in turn lead to better treatment success. Alternatively, treatments that are fixed and do not vary depending upon response are likely to lead to high drop out and poor response.

Learning Objectives:
• To learn about applied methods for adaptive research.
• To learn adaptations to enhance treatment retention.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

Workshop Overview

Nina R. Schooler, Ph.D.
VISN 5 MIRECC Washington DC Veterans Affairs Medical Center

Stephen R. Marder, M.D.
University of California, Los Angeles

Inadequate treatment of negative symptoms in schizophrenia is a significant public health issue. Although newer treatments for schizophrenia may have varying degrees of efficacy in treating these symptoms, elucidation of a regulatory path to an indication has been hindered by unresolved issues in clinical trial design. A major obstacle is the lack of consensus on the optimal measurement technique for assessing negative symptoms. Currently available measurement tools for negative symptoms vary widely in their face validity, psychometric properties, and user friendliness to the clinical trials investigator.

The goals of this session are to identify and more clearly define these hurdles and consider how they can be overcome in order to achieve a regulatory indication for treatment of negative symptoms in schizophrenia. The workshop will begin with a presentation, by Larry Alphs, providing an overview of clinical trial design methodological issues that impact assessment of efficacy for treating negative symptoms. Proposed solutions will be discussed. This will be followed by a critique of the validity, reliability, and ease of teaching of existing commonly used assessment tools for negative symptoms such as the BPRS, PANSS, and SANS, by Nina Schooler. Subsequently, there will be a presentation and discussion of the current status of an assessment tool for negative symptoms that is currently under development: the NIMH Working Group Negative Symptoms Scale, by Brian Kirkpatrick. This will be followed by a presentation of the psychometric properties and recent training and clinical trials experience of another relatively new scale in current use: The Negative Symptom Scale-16 (NSA-16), by David Daniel. A critique of clinical trials experience with each of the principal existing scales in clinical use will then be provided by Dawn Velligan.

The Workshop will conclude with both the FDA (Bob Levin) and NIMH (Wayne Fenton) perspectives on methodological considerations that must be addressed in order to establish monotherapy and augmentation indications for treatment of negative symptoms in schizophrenia. The general discussion will be led by Steve Marder.

Learning Objectives:
• Increase familiarity with key issues in the design of clinical trials to assess efficacy of treatments for negative symptoms.
• Increase familiarity with the psychometric properties and clinical utility of currently used rating scales for negative symptoms.
• Introduce newer scales for assessment of negative symptoms.
• Increase familiarity with regulatory issues in obtaining an indication for negative symptoms.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

Scales in Current Use: A Long-Term Perspective

Nina R. Schooler, Ph.D.
VISN 5 MIRECC Washington DC Veterans Affairs Medical Center

Although attention to negative symptoms as a treatment target represents a relatively recent development, clinical recognition of negative symptoms and their assessment is hardly new.

The currently out of favor diagnosis of "simple schizophrenia" provides a reasonable description of a "negative symptom" patient, albeit one who has never shown positive symptoms. In a more modern formulation, we recognize that negative symptoms may occur along with positive symptoms during an acute exacerbation, may persist after positive symptoms have remitted, may develop as positive symptoms remit, and may re-emerge as prodromal signs of an impending relapse.

Negative symptoms have been included as part of general scales of psychopathology, including the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS). The aptly named Scale for the Assessment of Negative Symptoms (SANS), the Schedule for the Deficit Syndrome (SDS), the Negative Symptom Assessment (NSA), and the ongoing NIMH Negative Symptoms Scale development represent efforts to focus specifically on negative symptom definition and assessment.

Other presentations in this workshop will focus on the NIMH initiative and the NSA. The goal of this presentation will be to review the other instruments mentioned and compare them in terms of utility for diagnosis, specific negative symptoms assessed, approach to assessment, and utility for assessing change in clinical trials.

Learning Objectives:
• Place current work on negative symptoms into a long-term frame of reference.
• Compare the BPRS, PANSS, SANS, and SDS in terms of approach to negative symptoms and coverage.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

Addressing Issues Relevant for Developing Broad Spectrum and Adjunctive Treatments of Negative Symptoms

Larry Alphs, M.D., Ph.D.
Pfizer, Inc.

Clinical trials that seek to demonstrate effectiveness of a treatment for alleviating negative symptoms of schizophrenia present a number of hurdles. This presentation will provide a clinical view on the objectives of clinical trials for treatment of negative symptoms, the hurdles they must address, and possible resolutions for them. Specifically, the presentation will address issues relevant for developing broad spectrum and adjunctive treatments.

Learning Objectives:
• Participants will become familiar with the issues and hurdles around the design of clinical trials to evaluate treatments for negative symptoms of schizophrenia.
• Participants will become familiar with the possible solutions to address the issues and hurdles in the design of clinical trials to evaluate treatments for negative symptoms of schizophrenia.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

The NIMH/MATRICS Process for Developing a Negative Symptom Rating Scale

Brian W. Kirkpatrick, M.D.
Medical College of Georgia

One of the recommendations that resulted from the NIMH-sponsored Consensus Development Conference on Negative Symptoms, held in January 2005, was that a new negative symptom rating scale appropriate for clinical trials be developed. The MATRICS process has subsequently sponsored the development of such a scale, and it is now close to entering field testing. Among the principles guiding the development of the scale are 1) subscales for the five domains named by the Consensus Statement on Negative Symptoms, i.e., alogia, blunted affect, avolition, anhedonia, and asociality; 2) omission of items related to attention and to disorganization of thought and behavior; 3) minimization of culture-bound questions and anchors; 4) separation of consummatory and anticipatory aspects of anhedonia; 5) obtaining feedback from the pharmaceutical industry as well as academicians in the field of schizophrenia research during the process of development; and 6) the expectation that the instrument will be modified substantially in response to the results of field testing. A summary of the scale's characteristics will be presented.

Learning Objectives:
• Participants will be able to state the purpose of the MATRICS scale development process.
• Participants will be able to name the five subscales to be included in the scale.
• Participants will be able to name two principles guiding the development of the scale.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

The Negative Symptom Scale-16 (NSA-16): Psychometric Properties and Recent Clinical Trial Experience of a Newer Negative Symptoms Instrument Measurement

David G. Daniel, M.D.
Global Learning, LLC

Lack of agreement among raters on measurement technique of negative symptoms is a source of non-specific variance in ratings that may diminish statistical power and increase the number of subjects required for a valid study. Achieving agreement among raters with respect to quantification of negative symptoms is particularly challenging when complicated by language differences and variations in cultural interpretation of symptoms, as may occur in international, multi-center clinical trials. To address this challenge, a scale should be well anchored, cross-culturally valid, and sensitive to change.

The Negative Symptom Assessment Scale (NSA) is a clinician-rated instrument for rating the negative symptoms of schizophrenia that attempts to address these needs. It contains 16 items plus a global score, and rates symptoms without consideration of etiology. It has been shown to have high inter-rater and test-retest reliabilities in English-speaking raters and high concurrent validity with similar instruments (Alphs, Summerfelt and Muller, 1989; Axelrod, Goldman and Alphs, 1993; Raskin et al, 1993; Axelrod and Alphs, 1993; Axelrod et al, 1994). It is sensitive to change and compares favorably in this respect to the BPRS retardation factor (Eckert et al, 1996). Using a confirmatory factor analytic procedure, a five-factor model emerged including Communication, Emotion/Affect, Social Involvement, Motivation, and Psychomotor activity (Axelrod, Goldman and Alphs, 1993). Each factor has 2-4 items, and anchors are identified for each item.

More recently, an analysis was conducted to assess whether high levels of agreement among raters across multiple nationalities and languages could be achieved in measurement of negative symptoms with the NSA. Raters from the United States and 18 other countries were trained to rate the NSA by viewing at least one training lecture and viewing and rating at least one videotaped, semi-structured NSA interview of a schizophrenic patient, followed by detailed feedback on the proper rating methods. Subsequently, raters were evaluated on their rating of an additional videotaped, semi-structured NSA interview of a schizophrenic patient. The raters consisted of two non-overlapping cohorts of multi-site international clinical trial investigators who were generally unfamiliar with the NSA prior to the training. The a priori measure utilized to evaluate acceptable agreement among raters was to score within one point of the modal score of their cohorts on at least 80% of the 16 NSA items. The same cohorts of raters were concurrently trained to rate the Positive and Negative Symptom Scale (PANSS) by a method analogous to that by which the NSA was taught. However, most raters had had previous training and experience in administering the PANSS to patients.

The results indicated that high levels of agreement in rating the NSA appear to be feasible among clinical trials raters from multiple countries. Training of multinational cohorts in rating the NSA appeared to be at least as successful as that of U.S. cohorts. Training in rating of the NSA appeared at least as successful as that for the PANSS.

Learning Objectives:
• Participants will become familiar with the background, content, format, and psychometric properties of the Negative Symptom Assessment Scale (NSA-16).
• Participants will become familiar with recent results of training sessions comparing agreement among a cross-cultural cohort of raters on the rating of the NSA-16 and PANSS.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

Use of Negative Symptom Assessments in Clinical Trials

Dawn I. Velligan, Ph.D.
University of Texas Health Science Center, San Antonio

Clinical trials to develop effective treatments for the negative symptoms of schizophrenia are important to pursue. A variety of instruments are available to measure negative symptoms, including the Scale for the Assessment of Negative Symptoms, the Negative Symptom Assessment, the negative items from the Positive and Negative Syndrome Scale, and the Schedule for the Deficit Syndrome. Scales differ in terms of the scope of symptoms assessed, the conceptualization of definition of symptoms, the domains captured, and their sensitivity to clinical changes. Issues to be resolved include the extent to which cognition and negative symptoms are separable domains, the extent to which improving negative symptoms impacts community outcomes, and the extent to which instruments that assess community functioning overlap with those assessing negative symptoms. We present data examining effect sizes for change on measures of negative symptoms and address methodological considerations in the selection of instruments.

Learning Objectives:
• Identify differences in commonly used assessments of negative symptoms.
• Identify problems with dimensions assessed by available negative symptom instruments as currently defined.
• Describe the sensitivity to change of various negative symptom assessments.

WORKSHOP 6

Negative Symptoms of Schizophrenia: Methodological Hurdles to Achieving an Indication
2:45 p.m. - 4:15 p.m.

FDA Perspective on Negative Symptoms in Schizophrenia as a Target for a Drug Treatment Claim

Robert L. Levin, M.D.
Food and Drug Administration

Negative symptoms are widely recognized as a feature of schizophrenia, and in fact are listed among the five characteristic symptoms of this disorder in DSM-IV. Furthermore, there seems to be general agreement that negative symptoms are an aspect of schizophrenia that do not respond adequately to currently available drug treatments. Thus, there is a compelling case for considering negative symptoms of schizophrenia as a possibly distinct target for drug development. The Food and Drug Administration (FDA) often faces the challenge of considering new clinical targets for drug development, and the purpose of this discussion is to elaborate on the thought process that FDA will undertake in considering negative symptoms of schizophrenia as a novel and distinct drug target.

Learning Objectives:
• Discuss the process of considering drug treatment targets.
• Discuss possible study designs for negative symptom trials.
• Discuss the complexity of measuring negative symptoms.
• Discuss challenges of analyzing data from negative symptom trials.

PLENARY SESSION

The Value and Limitations of Large Practical Clinical Trials in Informing Practice
8:45 a.m. - 11:50 a.m.

The Practitioner's Perspective

John M. Kane, M.D.
The Zucker Hillside Hospital and Albert Einstein College of Medicine

In discussing the value and limitations of large practical clinical trials in informing clinical practice, the first questions that we have to address are what kinds of information do practitioners really need, what information exists, what is missing, how do we fill the gaps, and how do we prioritize the importance of specific types of questions and data.

In the treatment of schizophrenia, clinicians are faced with a variety of decision points. What medication(s) are best for emergency management, acute treatment, continuation, and long-term treatment? How long is an adequate trial and at what dose? Should the dosage be increased and, if so, how high? Are combinations of medications indicated and, if so, for whom and for how long? What adverse effects are likely to occur and when can they be predicted, prevented, or managed? If not, when should treatment be changed and to what alternative?

The challenge in a large practical clinical trial is to frame an important question that can be answered in a clinically meaningful way: in other words, to study endpoints that are clinically relevant and to assess moderate treatment effects that would not necessarily have been detectable in a typical trial. This task is far more difficult than it first appears.

The results from the CATIE trial, for example, underscore the complexities in making treatment decisions when considering different types of patients at different phases of illness, while simultaneously attempting to understand dosage requirements and trying to balance both short-term and long-term benefits and risks.

Learning Objectives:
• To review the strengths and weaknesses of large pratical clinical trials in informing clinical practice.
• To discuss the treatment challenges facing practitioners and the kinds of data that they need.

PLENARY SESSION

The Value and Limitations of Large Practical Clinical Trials in Informing Practice
8:45 a.m. - 11:50 a.m.

Implications for Employer-Sponsored Health Services

Ron Finch, Ed.D.
National Business Group on Health

Pharmaceutical costs are increasing at unsustainable rates in employer-sponsored health services. Benefit managers are increasingly exploring new and practical solutions to controlling costs, increasing accuracy in prescribing, and promoting adherence. Controlling costs intersects with managing employee productivity. The aging workforce poses new challenges to controlling both costs and productivity.

Typically, benefit managers are not aware of the results of drug trials, depending on pharmacy benefit managers companies (PBMs) and pharmaceutical companies for information. Additionally, in many companies, pharmaceutical benefits are not integrated with health plan benefits, increasing the possibility that implications for healthcare providers may not be adequately addressed.

Currently, there are no formal or systematic approaches to translating results of drug trials. Benefit managers, medical directors, and other corporate healthcare workers could make practical application of this information in health plan design, disability management, and health promotion/well health programs.

Learning Objectives:
• Participants will learn that the costs of pharmaceutical benefits are increasing at an unsustainable rate.
• Participants will learn that employers are not typically aware of drug trial results.
• Participants will learn that there is no systematic approach to translating drug trial results for employers.

PLENARY SESSION

The Value and Limitations of Large Practical Clinical Trials in Informing Practice
8:45 a.m. - 11:50 a.m.

Through a Glass Darkly: A Patient/Advocate's Eye View of Large Clinical Trials

James P. McNulty, A.B.
National Alliance on Mental Illness

The presentation addresses the perspective and needs of patients, families, and advocates with respect to large clinical trials, and their implications for evidence-based treatments. The discussion addresses limitations of current treatments, including iatrogenic effects and the implications for adherence and long-term outcomes. We go on to discuss areas that need further consideration and research, using some of the findings of the Institute of Medicine's Quality Chasm series. We conclude by examining what might constitute successful treatment of mental illnesses from the patient and the family point of view, introducing recovery as a research tool and objective.

Learning Objectives:
• Participants will understand the patient/family perspective on research.
• Participants will understand how patients/families define success in treatment.
• Participants will understand how to frame research questions that are relevant to patients/families.
• Participants will understand the key concepts of recovery and their application to future research on mental illness.

NIMH REVIEW SESSION

NIMH Grants: Mock Review and Update on Electronic Submission of Grant Applications
12:30 p.m. - 2:00 p.m.

Henry J. Haigler, Ph.D.
National Institute of Mental Health

This session will be presented in three parts. The first part will be a brief overview of the grant receipt and referral process presented by Dr. Chris Sarampote. The second part of this session, directed by Dr. Henry Haigler, will be a "mock" review of three fictional grant applications (by Drs. Thisa Nogo, Justin Exemplar, and Joseph Sampler), with two of the chairs of standing review committees (Drs. Katharine Phillips and Mark Riddle) and staff members from the NIMH DEA participating as reviewers. This session will illustrate the grant review process based on the composite experience of all of the participants. The attendees will be asked to participate as members of the rest of the Initial Review Group (IRG) and ask any questions or participate in the discussion after the reviews have been presented. The third part of this session will be a brief description of the new process for the electronic submission of grant applications that is being used across NIH, by Dr. Jean Noronha, the Referral Officer for DEA at NIMH.

Learning Objectives:
• Participants will obtain a better understanding of the grant receipt and referral process at NIH/NIMH.
• Participants will obtain a better understanding and appreciation of the grant review process at NIH/NIMH.
• Participants will obtain a better understanding of the electronic grant submission process that is now being used for some NIH/NIMH applications; this process will be fully implemented by 2007.

PANEL 1

Use of SSRIs and Mood Stabilizers During Pregnancy: Weighing the Risks
2:00 p.m. - 4:00 p.m.

Panel Overview

Lee S. Cohen, M.D.
Massachusetts General Hospital and Harvard Medical School

Mood disorders are highly prevalent and cluster in women of reproductive age. Given increased awareness and treatment of affective disorders in the community, growing numbers of women seek consultation regarding the relative risks of prenatal exposure to medications such as antidepressants and mood stabilizers; they also seek information regarding risk for relapse of psychiatric disorder associated with discontinuation of these medications during pregnancy. Over the last decade, multiple reports on the reproductive safety of antidepressants have appeared in the literature, particularly for the selective serotonin reuptake inhibitors (SSRIs) and certain mood stabilizers including lithium, sodium valproate, and lamotrigine. Until relatively recently, studies of the reproductive safety of SSRIs have been relatively reassuring. However, recent reports have raised concerns regarding 1) the potential teratogenicity of certain SSRIs, 2) risk for a putative neonatal distress syndromes associated with SSRI use during the peripartum period, and 3) question of increased risk for persistent pulmonary hypertension of the newborn following late-pregnancy exposure to SSRIs. Accumulating data regarding the reproductive safety of SSRIs has been paralleled by growing availability of global teratovigilance data regarding commonly used mood stabilizers such as sodium valproate and lamotrigine. This series of presentations will review available data regarding the reproductive safety of SSRIs and mood stabilizers so those who manage patients treated with these agents can more completely inform them about the relative risks of fetal exposure to such medicines. Response to emerging data on reproductive safety data by federal regulators will also be discussed. Lastly, a conceptual framework for integrating the evolving information regarding risks of prenatal exposure to psychiatric medications will be presented.

Learning Objectives:
• Participants will gain an understanding of the newest data regarding the reproductive safety of SSRIs.
• Participants will learn about the emerging teratovigilance data for mood stabilizers, with a special focus on antiepileptic drug registries which monitor outcomes of prenatal exposure to these medicines.
• Participants will develop an appreciation of the regulatory issues involved as reproductive safety data emerges over time for medications such as antidepressants and anticonvulsants.

PANEL 1

Use of SSRIs and Mood Stabilizers During Pregnancy: Weighing the Risks
2:00 p.m. - 4:00 p.m.

Including Human Data in Drug Product Labels: A Conceptual Framework

Kathleen Uhl, M.D.
Food and Drug Administration

The FDA is working to improve prescription drug labeling related to drug use and drug exposure during pregnancy. The pregnancy section of drug labels usually contains only animal data and is rarely updated to include human experience with the product as it evolves after marketing approval. The inclusion of appropriate human pregnancy exposure data in product labeling requires careful analysis and interpretation of data and the appropriate communication of results, including risk information, in labeling. Examples of labels that have been updated with human pregnancy data demonstrate the inherent challenges with pregnancy labeling. FDA's efforts to revise the regulations that govern pregnancy labeling will be discussed. The inclusion of clinically relevant human pregnancy data in drug labeling will assist health care providers and their patients when making decisions regarding the use of drugs in pregnancy and will provide useful information for treating or counseling patients who are pregnant or anticipating pregnancy.

Learning Objectives:
• Understand informational elements regarding drug exposure and use in pregnancy that are important to drug labeling.
• Become aware of upcoming changes to the pregnancy section of labeling.
• Demonstrate examples of the pregnancy section of drug labels that include human pregnancy data.

PANEL 2

Research Advances in the Treatment of Major Depression in Children and Adolescents
2:00 p.m. - 4:00 p.m.

Panel Overview

Benedetto Vitiello, M.D.
National Institute of Mental Health

This panel will present and discuss new research on the effectiveness of antidepressant treatments for children and adolescents with depressive disorders. Three presentations will be made. First, Dr. March will present the 9-month outcome results of the Treatment for Adolescents with Depression Study (TADS). TADS is a publicly funded randomized trial to test the effectiveness of fluoxetine, cognitive-behavioral therapy (CBT), and their combination in adolescents with major depressive disorder. The 3-month outcome results have been published, showing the effectiveness of fluoxetine, alone or in combination with CBT. The focus on this presentation will be the outcome data through the entire 9 months of treatment. Then, Dr. Emslie will discuss the recently concluded federally-funded relapse prevention trial testing the long-term efficacy of fluoxetine compared with placebo in about 100 children and adolescents (age 8 to 18 years) who had improved during acute open-label treatment. Finally, Dr. Vitiello will provide an update on the Treatment of Resistant Depression in Adolescents study (TORDIA). TORDIA is a randomized, multi-site trial currently in progress to test the effectiveness of second-step interventions (antidepressants alone or in combination with CBT) for adolescents whose depression had proved resistant to an adequate trial of selective serotonin reuptake inhibitor medication.

Learning Objectives:
• To learn of the current evidence of the efficacy and safety of antidepressant treatments for adolescents with major depressive disorder.
• To learn of the efficacy of long-term treatment for prevention of relapse pediatric major depression.
• To learn of the research currently in progress on the effectiveness of pharmacological and combined treatments for treatment-resistant adolescent depression.

PANEL 2

Research Advances in the Treatment of Major Depression in Children and Adolescents
2:00 p.m. - 4:00 p.m.

Treatment for Adolescents with Depression Study (TADS): Longer-Term Outcomes

John S. March, M.D.
Duke University Medical Center

The Treatment for Adolescents with Depression Study (TADS) evaluates the effectiveness of four treatments for adolescents with MDD: clinical management with fluoxetine (FLX), cognitive-behavior therapy (CBT), their combination (COMB), and clinical management with placebo (PBO). We previously reported (TADS Team, JAMA, 292: 807-20) that COMB and FLX were more effective than CBT or PBO after 12 weeks of acute treatment, with a response rate of 71% for COMB, 61% for FLX, 43% for CBT, and 35% for PBO. Across nine months of randomized treatment, all three active treatments produced robust improvements. Relative to CBT, COMB showed a larger and more persistent benefit than FLX. Rates of response at week 18 were: COMB 85%, FLX 69%, and CBT 65%. Rates of response at week 36 were: COMB 86%, FLX 81%, and CBT 81%. Clinically significant suicidal ideation decreased substantially with treatment, but less so with FLX than with COMB or CBT. Approximately 10% of patients experienced a treatment-emergent suicidal event. Suicidal events were more common in patients treated with FLX (14.7%) than with COMB (8.4%) or CBT (6.3%). Thus, combined treatment accelerates recovery relative to CBT and FLX alone and minimizes the risk of suicidality relative to FLX alone. Taking benefit and risk into account, the combination of fluoxetine and CBT appears superior to either monotherapy as a treatment for moderate to severe MDD in adolescents.

Learning Objectives:
• Understand the design of the TADS.
• Understand the TADS sampling frame / sample.
• Understand the short- and long-term outcomes.
• Understand the public health implication of the TADS.

PANEL 2

Research Advances in the Treatment of Major Depression in Children and Adolescents
2:00 p.m. - 4:00 p.m.

Fluoxetine vs. Placebo for Continuation Treatment of Pediatric MDD

Graham J. Emslie, M.D.
University of Texas Southwestern Medical Center

Background: Recent research has demonstrated positive efficacy of several selective serotonin reuptake inhibitors (SSRIs) in treating depression in the pediatric age group. In these randomized, controlled, acute trials, around 50-60% of youth respond to antidepressant treatment. Yet, how long to continue antidepressant treatment in this age group remains a question. Adult research suggests continuation treatment for 3-9 months following acute treatment response. Only one small trial to date has compared antidepressant treatment and placebo in this age group. In this small study (n=40), subjects remaining on fluoxetine were less likely to relapse than subjects on placebo, and time to relapse was shorter for those on placebo.

Method: One hundred two subjects who responded to 12 weeks of open label treatment with fluoxetine (10-40mg) were randomized to continued fluoxetine treatment (n=50) or switch to placebo (n=52) for 6 months. Primary outcome was relapse (defined as CDRS-R≥40 with a 2-week deterioration of mood symptoms) or clinical deterioration based on clinical assessment.

Results: Forty-two percent (n=21) of subjects on fluoxetine experienced a relapse or significant clinical deterioration, compared to 69% (n=36) on placebo (p=0.005). Only 22% (n=11) of subjects on fluoxetine met the stricter criteria of pure relapse (CDRS-R ≥40 with 2 weeks of worsening of depression), compared to 48% (n=25) on placebo.

Conclusion: Continued treatment with fluoxetine prevents relapse in children and adolescents with MDD.

Learning Objectives:
• To present data on the open-label treatment phase of 168 children and adolescents with MDD treated with fluoxetine.
• To present findings from the first large randomized, double-blind, placebo-controlled continuation trial of fluoxetine in pediatric MDD.

PANEL 2

Research Advances in the Treatment of Major Depression in Children and Adolescents
2:00 p.m. - 4:00 p.m.

The Treatment of Resistant Depression in Adolescents (TORDIA) Study: A Research Update

Benedetto Vitiello, M.D.
National Institute of Mental Health

In adolescent depression, the response rate after a single trial of antidepressant medication is about 50-60%, often with incomplete remission, thus making it clinically important to develop effective second-step interventions. The Treatment of Resistant Depression in Adolescents (TORDIA) study is a publicly funded, multisite, randomized clinical trial testing the effectiveness of alternative treatments for adolescents (age 12-18 years) with major depressive disorder, dysthymia, or depression NOS still suffering from depression (as shown by a Child Depression Rating Scale-Revised total score of 40 or greater) after adequate treatment with a selective serotonin reuptake inhibitor (SSRI). An adequate trial of SSRI is defined as treatment for at least 6 weeks, of which 2 weeks were on a daily dose of at least 40 mg of fluoxetine (or equivalent other SSRI). Patients are randomly assigned to receive one of four possible treatments for 12 weeks: 1) an alternative SSRI (citalopram for those who had received fluoxetine, fluoxetine for those who had received citalopram or escitalopram, and randomly selected fluoxetine or citalopram for those who had received fluvoxamine); 2) a different type of antidepressant (i.e., venlafaxine); 3) an alternative SSRI plus cognitive-behavioral therapy (CBT); or 4) venlafaxine plus CBT. The study is conducted at the University of Pittsburgh (PI: David Brent), Southwestern Medical Center in Dallas (PI; Graham Emslie), Kaiser Permanente in Portland, OR (PI: Gregory Clarke), UCLA (PI: Joan Asarnow), Brown University (PI: Martin Keller), and University of Texas in Galveston (PI: Karen Wagner). Enrollment into the study started in 2001 and will be completed (N=400) in 2006. As of February 2006, 311 patients had been randomized. This presentation will provide an update on the status of the project and describe the impact of regulatory safety warnings about SSRI use in youth on patient recruitment into this study.

Learning Objectives:
• To learn of research currently in progress on the effectiveness of pharmacological and combined treatments for treatment-resistant adolescent depression.
• To learn of approaches to optimize pharmacological treatment of adolescent depression.
• To learn of the impact on research of safety concerns about antidepressant use in youths.

PANEL 3

STAR*D — What Have We Learned?
2:00 p.m. - 5:00 p.m.

Panel Overview

A. John Rush, M.D.
University of Texas Southwestern Medical Center

This panel will present the overall acute treatment results (symptom and function) and selected results from the 1-year naturalistic follow-up from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Dr. Fava will present the overall study design and rationale. Dr. Rush will present the Level 1 (citalopram) acute findings, including cumulative response and remission rates, moderators of response and remission, and relapse findings for those who entered follow-up who remitted and who responded but who did not remit. Dr. Rush will present analogous results from patients entering Level 2 medication switch and augmentation treatments. Dr. Thase will present Level 2 acute and long-term results among those who reveived cognitive therapy as switch or augmentation at Level 2. Dr. Nierenberg will present similar results from Level 3 augmentation and switch subjects including long-term follow-up results. Dr. Stewart will present the Level 4 acute and longer-term findings. Discussion will focus on the implications of these findings for both future clinical trials and for clinical practice.

Learning Objectives:
- Participants will learn the results of the acute phase treatments used in the STAR*D trial for treatment-resistant depression.
- Participants will learn the result of the long-term naturalistic follow-up for depressed patient treatment in the STAR*D trial.

PANEL 3

STAR*D — What Have We Learned?
2:00 p.m. - 5:00 p.m.

Overview of STAR*D Study Design

Maurizio Fava, M.D.
Massachusetts General Hospital

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study used a prospective design to determine the comparative effectiveness of different next-step treatment options for outpatients with major depressive disorder (MDD) when remission was not attained with an initial selective serotonin reuptake inhibitor (SSRI), citalopram (CIT). In addition, STAR*D utilized a novel approach, which we called the "equipoise stratified" design, that allowed flexibility in the randomization process, so that both study participants and clinicians had some say as to which treatment options a given study participant was randomized to. Clinical outcomes of STAR*D were very broad and included symptoms, function, side effect burden, quality of life, and participant satisfaction. These outcomes were evaluated by independent assessors masked to treatment assignments or by an IVR system. This presentation will review the unique and innovative aspects of the design and methodology of STAR*D; it also will present the general characteristics of the population enrolled in STAR*D, which enrolled "real world" adults (ages 18-75) with MDD from both primary and specialty care practices.

References:
Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, Kupfer DJ. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am. 2003 Jun;26(2):457-94.

Lavori PW, Rush AJ, Wisniewski SR, Alpert J, Fava M, Kupfer DJ, Nierenberg A, Quitkin FM, Sackeim HA, Thase ME, Trivedi M. Strengthening clinical effectiveness trials: equipoise-stratified randomization. Biol Psychiatry. 2001 Nov 15;50(10):792-801.

Learning Objectives:
• Participants will become familiar with the overall design and methods of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.
• Participants will learn the general characteristics of the population enrolled in STAR*D, which enrolled "real world" adults (ages 18-75) with MDD from both primary and specialty care practices.

PANEL 3

STAR*D — What Have We Learned?
2:00 p.m. - 5:00 p.m.

What Were the Acute and Long-Term Outcomes of Level 1?

Madhukar H. Trivedi, M.D.
University of Texas Southwestern Medical Center

Over 2870 depressed outpatients entered citalopram treatment delivered under a Measurement-Based Care approach. The method acquires the systematic evaluation of symptoms by the Quick Inventory of Depressive Symptoms-Clinician Rating (QIDS-C) and the Frequency, Intensity, and Side Effect Burden Rating (FIBSER) at each treatment visit. In addition, guidelines as to when/how to adjust medication dosing based on the QIDS-C and FIBSER ratings were provided. A clinical research coordinator assisted in patient management. The trial allowed up to 14 weeks of medication treatment, with an optional triage point at 8-9 weeks should minimal symptom reduction have occurred at the maximally tolerated dose.

Results of this Level 1 acute trial revealed a 30-33% remission rate. Furthermore, about 1/3 of those who did ultimately respond did so after 6 weeks, and about half of those who ultimately remitted did so after 6 weeks. Data to identify baseline features most likely associated with remission, and the longer-term outcomes in the 12-month follow-up will be presented.

Learning Objectives:
• Participants will understand the methods entailed in measurement-based care.
• Participants will be able to identify clinical relevant baseline predictors of remission with citalopram.

PANEL 3

STAR*D — What Have We Learned?
2:00 p.m. - 5:00 p.m.

STARD*D Level 2 Acute and Longer-Term Outcomes with Cognitive Therapy

Michael E. Thase, M.D.
University of Pittsburgh School of Medicine

This presentation will highlight the results of three aspects of the STAR*D project: 1) results of the Level II randomized comparisons involving Cognitive Therapy, both alone and as an augmentation strategy, following nonresponse to citalopram; 2) results of the Level IV randomized comparison of a combination of two newer antidepressants (mirtazapine plus venlafaxine) versus an older, nonselective/irreversible monoamine oxidase inhibitor (tranylcypromine); and 3) results of the one year follow-up of all patients who responded to any level of therapy in STAR*D. An embargo imposed by the study's sponsor, the National Institute of Mental Health, precludes summarizing any of the STAR*D study's findings in abstract form prior to publication. Nevertheless, all three phases of the study are complete, data from the Level II and Level IV studies are analyzed and manuscripts have been drafted, and, at the time of presentation, data from the follow-up phase will be analyzed and ready for presentation. These data—which are from the largest studies ever undertaken to examine the role of psychotherapy in antidepressant nonresponders and, for patients with more advanced levels of treatment resistance, to compare one of the more highly regarded newer strategies (the combination of mirtazapine and venlafaxine) with one of the older standards (the MAOI tranylcypromine)—provide important new information to guide the treatment of patients with difficult-to-treat depression.

Learning Objectives:
• Participants will become familiar with the various treatment strategies for resistant depression.
• Participants will become familiar with the results of the study and psychotherapy alone vs. combination therapy.

PANEL 3

STAR*D — What Have We Learned?
2:00 p.m. - 5:00 p.m.

STAR*D Level 4 Acute and Long-Term Outcomes

Jonathan W. Stewart, M.D.
Columbia University

Altogether, 109 patients enrolled in the STAR*D Level 4 acute treatment trial. For all enrollees, this represented the fourth medication treatment attempt, with the prior three ending either in nonremission and/or intolerance. For a very few, cognitive therapy (either as a switch or augmentation to citalopram) had not been adequate.

Patients were randomized to one of two switch medication options (to either the MAOI tranylcypromine or a combination of both mirtazapine and venlafaxine-XR). Both treatment options have been thought to be useful in more treatment resistant depression.

The clinical and demographic features of the very treatment resistant populations will be described. Outcome results will be presented in terms of the acute trial (symptom effects, tolerability, safety), and the overall longer-term symptomatic outcomes.

Learning Objectives:
• Participants will learn whether MAOIs are more effective than a combination of two antidepressant medications in treatment-resistant depressed patients.
• Participants will be able to evaluate the longer-term outcomes for patients who at least respond to their fourth medication trial.

UPDATE SESSION I

4:15 p.m. - 5:15 p.m.

Relapse Prevention After Somatic Treatments

Charles H. Kellner, M.D.
University of Medicine and Dentistry of New Jersey, New Jersey Medical School

George Petrides, M.D.
University of Medicine and Dentistry of New Jersey, New Jersey Medical School

This workshop will explore the uses of ECT, TMS, VNS and CBT in the prevention of relapse of recurrent depressive illness. New data and reviews of existing literature will be presented.

Learning Objectives:
• Understand the use of C_ECT.
• Know the status of VNS therapy.
• Know the status of TMS therapy.
• Be familiar with the role of CBT in relapse prevention.

UPDATE SESSION I

4:15 p.m. - 5:15 p.m.

Have Maintenance Studies of Antidepressant Prophylaxis Against Recurrence Been Incorrectly Designed?

Mark Zimmerman, M.D.
Rhode Island Hospital

The return of symptoms of depression after a period of improvement lasting for a short time (less than six months) is referred to as a relapse, whereas symptom return after a prolonged period of improvement (more than six months) is considered a recurrence. At a conceptual level, relapse is considered the return of symptoms of the index episode which never resolved at a pathophysiological level, whereas recurrence is thought of as the onset of a new episode following the resolution of the underlying biology of the index episode. Because no biological state markers are available to monitor the course of depression, it is not possible to determine when an episode has biologically ended. Consequently, the distinction between relapse and remission is based on the duration of symptom improvement and resolution.

One would predict the likelihood of symptom return after a brief period of wellness to be higher than the likelihood after a sustained period of wellness. That is, the rate of relapse during continuation treatment should be higher than the rate of recurrence during maintenance treatment. However, a review of continuation and maintenance studies of antidepressant medications finds that the rate of relapse and recurrence after switching patients from active medication to placebo is identical. This suggests that there is a problem in the differentiation of relapse from recurrence in continuation and maintenance studies of antidepressants. Specifically, it is likely that in maintenance studies, symptom reemergence represents a combination of both relapses and recurrences. We describe a modification to the design of maintenance studies of antidepressants so that these studies more validly examine recurrence rates rather than a combination of relapse and recurrence rates.

Learning Objectives:
• Understand the distinction between continuation and maintenance studies of antidepressant medication.
• Understand the distinction between relapse and recurrence.
• Understand why the equal prevalence of relapse and recurrence rates in continuation and maintenance studies challenges the validity of the distinction between these concepts.
• Describe a modification of the traditional maintenance study design to improve validity of these studies.

UPDATE SESSION I

4:15 p.m. - 5:15 p.m.

Exercise in the Treatment of Major Depressive Disorder: Efficacy, Mechanisms, and Cardiovascular Disease

Madhukar H. Trivedi, M.D.
University of Texas Southwestern Medical Center

Exercise has been shown to alleviate depressive symptoms in clinical and subsyndromal depression. Recent evidence has shown that aerobic exercise, when conducted at a dose consistent with public health guidelines, is an effective monotherapeutic treatment for major depressive disorder. Further evidence suggests that exercise may be an effective augmenting strategy for depression in partial responders to antidepressant pharmacotherapy. The Treatment with Exercise Augmentation for Depression (TREAD) study is a randomized, controlled trial that is currently underway to investigate the use of exercise as an augmentation in patients with residual symptomatology following an adequate trial of selective serotonin reuptake inhibitor (SSRI) treatment. In addition to its efficacy, exercise is an attractive candidate for the treatment of major depressive disorder for a number of reasons, including patient desirability, a reduced likelihood of adverse treatment effects (particularly compared with pharmacological treatment), and numerous benefits to overall health. Neuroscientific evidence suggests plausible biological mechanisms through which exercise may yield antidepressant effects, as well as potentiate effects of antidepressant pharmacotherapy.

Depression not only adversely affects emotional, cognitive, and social function; it also is a risk factor for cardiovascular disease. A variety of different mechanisms have been suggested to explain this relationship. Because of the impact of depression and its relationship with cardiovascular risk factors on overall health and well-being, it is crucial to better understand and develop treatment approaches, such as exercise, that improve depressive symptoms as well as indices of cardiovascular health and metabolic function. This panel will review current data on treatment efficacy, cardiovascular risk factors associated with MDD, and the mechanisms by which exercise may be beneficial both to symptomatic relief in depression as well as improvements in cardiovascular status.

Learning Objectives:
• Review current efficacy data on ongoing research using exercise as a treatment for major depressive disorder.
• Discuss mechanisms by which exercise potentially elicits antidepressant effects and augments the effects of antidepressant medications.
• Review cardiovascular risk factors associated with depression and suggested relevant mechanisms for this relationship.

UPDATE SESSION II

4:15 p.m. - 5:45 p.m.

The Complex Challenge of Co-morbid Psychiatric and Alcohol Use Disorders

Mark L. Willenbring, M.D.
National Institute on Alcohol Abuse and Alcoholism

Co-morbid psychiatric disorders are common among individuals with alcohol use disorders (AUDs), and their co-occurrence presents challenging obstacles to successful management. The complex relationship between psychiatric and alcohol use disorders begins early in life. They share genetic and other risk factors, and mental disorders among children are one of the primary risk factors for developing alcohol use disorders during adolescence. In adults, the risk for other psychiatric disorders among people with alcohol dependence is 3 to 7 times higher than in people without alcohol dependence.

The presence of both psychiatric and substance use disorders magnifies the challenges to successful management of either disorder for providers as well as for patients, their loved ones, and for society at large. Many cases of harmful drinking and alcohol dependence eventually resolve without treatment, but it is likely that those which become chronic have a higher rate of psychiatric disorders. People seeking treatment for alcohol dependence also have more co-morbidity than those who do not. Outcomes for both types of disorders are poorer when they co-occur than when they do not.

Unfortunately, the treatment systems for each are not well-integrated, and neither is well-integrated with the general medical care system. General medical and psychiatric providers do a poor job of identifying and addressing heavy drinking, and most alcohol treatment programs lack staff skilled in diagnosing and treating mental illnesses. Thus, it is rare to have mental, addiction, and medical problems treated simultaneously and in a coordinated fashion. That said, treatment for co-occurring disorders lacks a well-defined evidence base. There is evidence that addressing alcohol dependence in the context of assertive community treatment for serious and persistent mental illness is helpful, but there is a lack of randomized controlled trials demonstrating clear benefit. Integration strategies appear to offer benefit at least for coordination of care and patient satisfaction, even if patient-level outcomes are more difficult to change. Treatment of depressed alcohol-dependent persons is similarly unclear, with some trials of antidepressants demonstrating efficacy, while others have not. The way in which pharmacotherapy for alcohol dependence should be integrated with psychiatric care has not been well-studied. There is evidence that valproate is effective in combined alcohol dependence and bipolar disorder. Until further evidence becomes available, treatment of co-occurring disorders will need to be based upon clinical experience and common sense.

Research is badly needed on treatment of the wide range of mental disorders in conjunction with alcohol use disorders. Particular areas of need include schizophrenia, bipolar disorder, depression, social anxiety disorder, eating disorders, and personality disorders. Research is needed not only on how to treat the alcohol dependence, but how to treat the psychiatric disorders that occur with it as well. For example, clinicians are frequently confronted with difficult decisions concerning pharmacotherapy for psychiatric disorders in the face of continued heavy drinking. Health services research is needed on configuration of services and benefits for various combinations of disorders. Finally, more work is needed on disease management strategies for treating chronic co-occurring disorders.

Learning Objectives:
• Recognize the prevalence, impact, and economic consequences attributed to co-occurring alcohol problems and psychiatric disorders.
• Discuss the complex issues associated with recognizing and differentiating alcohol dependence from psychiatric disorders.
• Examine the role of pharmacotherapy for maintaining abstinence in patients with co-morbid psychiatric disorders.

UPDATE SESSION II

4:15 p.m. - 5:45 p.m.

The Rise and Fall of the DST

Edward Shorter, Ph.D.
University of Toronto

The discovery that hypercortisolemia was as characteristic of patients with severe mood disorders, as those with Cushing's disease, led to the development of a formal test of the dysfunction: the dexamethasone suppression test (DST). Many studies in the 1960s and 1970s supported the test as a measure of endogeneity. It was a state marker that identified responsive populations to antidepressant treatments. It normalized with successful treatment and became abnormal again with relapse.

Following the introduction of DSM-III, questions arose as to the test's diagnostic specificity and validity. An NIMH workshop in 1982 and an APA Task Force in 1986 concluded that the test was an interesting scientific study but had limited clinical applicability.

Recent interest in hypercortisolemia has led to an improvement in the test, the DEX/CRH modification.

Dissatisfaction with the DSM classification has led to essays on reviving the concept of Melancholia in DSM-V. These essays assess a central role for tests of cortisol metabolism and encourage a re-visit to the DST, its rejection, and its role in a reclassification of depressive mood disorders.

Learning Objectives:
• Discuss hypercortisolemia as a measure of depressive illness.
• Discuss the merits of the DST (and DEX/CRH) tets for diagnosis.
• Discuss an approach to re-classification of depressive illnesses.

UPDATE SESSION II

4:15 p.m. - 5:45 p.m.

Managing Somatic Presentations of Mental Disorders

Javier I. Escobar, M.D.
University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School

Patients presenting with high levels of unexplained physical symptoms are a frequent, frustrating, and costly reality in general health and mental health care settings. Unfortunately, few effective interventions have emerged from controlled clinical trials. This presentation will provide an update of recent research in this area, including work on full DSM-IV Somatization Disorder, Hypochondriasis, and Somatic Manifestations of Common Mental Disorders in Primary Care. These interventions have centered around a non-pharmacological (CBT-type) approach that has been well adapted for various populations. These data come from large, controlled, NIMH-funded studies. The results of these studies look very promising, seem cost-effective, and may change the ways these patients are managed, particularly in primary care settings. This update will also include a brief historical review of the field and a brief description of diagnostic proposals being made for DSM-V.

References:

1. Lamberg L, "New Mind/Body Tactics Target Medically Unexplained Physical Symptoms and Fears", JAMA, 294: 2152-2154, 2005
2. Escobar JI, and Gara M, "DSM-IV Somatoform Disorders: Do we Need a New Classification?", General Hospital Psychiatry, 21: 154-156, 1999.

Learning Objectives:
• Understand the relevance of unexplained physical symptoms to psychopathology.
• Recognize new effective interventions for somatoform disorders.
• Conceptualize these syndromes more effectively.

PANEL 4

Translational Research in Geriatric Psychiatry: Implications for Symptomatic and Preventative Interventions
9:00 a.m. - 11:00 a.m.

Panel Overview

Gwenn S. Smith, Ph.D.
The Zucker Hillside Hospital and Albert Einstein College of Medicine

The integration of genetic, neuropsychological, and neuroimaging approaches to understanding affective symptoms and cognitive impairment in the elderly may potentially lead to novel therapeutic and prevention strategies for such clinically challenging problems as treatment-resistant depression and the detection of cognitive impairment related to Alzheimer's disease and the implementation of strategies to slow disease progression. The speakers in the session are investigators who have applied genetic, neuropsychological, and/or neuroimaging methods to understand the neurobiological basis of affective and cognitive symptoms, with the ultimate goal of informing pharmacotherapy. Dr. Helen Lavretsky will present her research that has focused on methylphenidate augmentation of SSRI treatment and the role of dopamine and serotonin polymorphisms in symptomatic and cognitive responses to treatment. Dr. Francis Lotrich will present his work involving the integration of genetic measures into a clinical trial of interferon to determine the genetic polymorphisms that affect vulnerability to the development of depressive symptoms. Dr. Natalie Rasgon will discuss neuroimaging studies of the neuroprotective effects of estrogen that will have implications for preventative interventions in neurodegenerative diseases. Dr. Herb Harris will discuss the implications of the genetic and neuroimaging findings presented for drug development.

Learning Objectives:
• To understand the role of the dopamine system in geriatric depression.
• To understand the relationship between depressive symptoms and inflammatory disorder using interferon treatment as a model.
• To understand the role of genetic and neuroimaging biomarkers in Alzheimer's Disease and mild cognitive impairment.
• To become familiar with the available medications to treat depression and cognitive deficits in dementia and with the areas of new medication development.

PANEL 4

Translational Research in Geriatric Psychiatry: Implications for Symptomatic and Preventative Interventions
9:00 a.m. - 11:00 a.m.

Dopamine Transporter Genetic Polymorphism was Associated with Preferential Treatment Response to Methylphenidate Combined with Citalopram in Geriatric Depression: A Pilot Study

Helen Lavretsky, M.D.
Semel Institute for Neuroscience and Human Behavior at University of California, Los Angeles

Objectives: The authors examined the role of the dopamine and serotonin transporter polymorphisms in clinical and cognitive features of subjects with late-life depression, and in preferential treatment response to the combination of methylphenidate and citalopram.

Methods: The authors studied 15 outpatients with current episodes of non-psychotic major depression in a ten-week double-blind trial of methylphenidate combined with citalopram and compared to citalopram and placebo. Response was defined as a score on the Hamilton Depression Rating Scale (24-item) of less than 10. All underwent genotyping to determine the dopamine (DAT VNTR) and serotonin (5-HTTLPR) transporters' polymorphisms.

Results: Subjects homozygous by DAT VNTR-10 genotype had greater impairment in executive cognitive tests at baseline compared to others. However, they responded preferentially to methylphenidate administered with citalopram with a greater reduction in depression severity over time and improvement in cognitive tests of executive function compared to other subjects. The 5-HTTLPR s-allele carriers had a faster onset of antidepressant response than non-carriers, but they demonstrated no difference in the overall response or cognitive improvement with treatment.

Conclusion: DAT VNTR 10/10 genotype may be associated with an endophenotype of late-life depression associated with executive dysfunction that responds preferentially to methylphenidate added to a standard antidepressant that requires replication in a larger sample.

Learning Objectives:
• Participants will learn about the clinical features and patterns of treatment response in geriatric depression.
• Participants will learn about the rationale for methylphenidate and psychostimulant use in geriatric depression.
• Participants will learn about the differential response to methylphenidate combination with citalopram based on the dopamine transporter genotype.

PANEL 4

Translational Research in Geriatric Psychiatry: Implications for Symptomatic and Preventative Interventions
9:00 a.m. - 11:00 a.m.

Genetic Vulnerability, Interferon-Alpha, and Depression

Francis E. Lotrich, M.D., Ph.D.
Western Psychiatric Institute and Clinic,University of Pittsburgh School of Medicine

Anhedonia, fatigue, and other physical complaints can often be prominent in late-life depression. There is increasing evidence that some inflammatory cytokines can induce this constellation of symptoms and that they may play a role in severe mood disorders. In particular, interferon-alpha has been implicated as a substance capable of inducing major depression. However, vulnerability to developing interferon-induced depression may have a genetic component. Understanding the interacting relationship between genetic vulnerability, the serotonergic system, and the psycho-neurologic effects of inflammatory cytokines may be important in delineating the etiology of major depression. Recent findings in this area will be reviewed.

Learning Objectives:
• Understand recent findings relating interferon-alpha and depression.
• Understand how genetic vulnerability may influence sensitivity to cytokines in depression.

PANEL 4

Translational Research in Geriatric Psychiatry: Implications for Symptomatic and Preventative Interventions
9:00 a.m. - 11:00 a.m.

Educational Translational Research in Geriatric Psychiatry: Implications for Symptomatic and Preventative Interventions

Natalie K. Rasgon, M.D., Ph.D.
Stanford University School of Medicine

This presentation will review data culled from recent studies of cognitive performance and regional cerebral metabolism in persons at genetic and familial risk for Alzheimer's disease (AD). We used positron emission tomography to evaluate cerebral glucose metabolic change in postmenopausal estrogen users and non-users in a 2-year naturalistic observational study. Region of interest (ROI) analysis revealed a significant decrease in metabolism of the posterior cingulate cortex among non-users at 2-year follow-up. In contrast, women estrogen users did not exhibit significant metabolic change in the posterior cingulate. These findings on the decline in the posterior cingulated are interesting, as apolipoprotein E-4 (APOE-4) is associated with lowered parietal, temporal, and posterior cingulated cerebral glucose metabolism in patients with a clinical diagnosis of AD. These findings will be discussed, in addition to endocrine and metabolic correlates contributing to risk of AD.

Learning Objectives:
• Inform participants about research related to cognitive performance and brain imaging in patients at risk for AD.
• Educate participants about endocrine and metabolic correlates contributing to risk of AD.

PANEL 5

Assessment and Prediction of Antipsychotic Drug Response
9:00 a.m. - 11:00 a.m.

Panel Overview

Anil Malhotra, M.D.
The Zucker Hillside Hospital

There is marked heterogeneity in response to antipsychotic drug treatment, ranging from subjects who respond within days to treatment to patients who never achieve symptom remission. Moreover, it is becoming increasingly evident that early response to antipsychotic drug treatment may be important from the clinical practice perspective, as well as have important implications for long-term outcome. Critical issues in identifying mediators of antipsychotic drug response include: assessment measures used to quantify clinical response, the clinical variables that most strongly influence drug response, and the identification of biological predictors of drug efficacy and effectiveness. In this panel, we will present data that suggest that a number of factors are involved in the assessment and prediction of antipsychotic drug response, including clinical, neurocognitive, and genetic factors. John Kane will present data on new approaches to defining and predicting treatment response in longitudinal studies and address questions on the length of an adequate clinical trial and comprehensive measurement strategies to assess response. Terry Goldberg will present data on the utilization of neurocognitive task performance as outcome measures in clinical trials, and discuss the evidence that neurocognition can be used to predict antipsychotic drug response in schizophrenia. Anil Malhotra will describe the use of molecular genetic approaches to predicting drug efficacy and drug-induced side effects, including new data from a recently completed pharmacogenetic study in first-episode schizophrenia. Finally, we will invite additional participation from investigators involved in assessing the potential that neuroimaging parameters may have in this domain. Taken together, we hope that this panel will provide an overview of the current issues in the assessment of antipsychotic drug response, provide novel data on the prediction of antipsychotic drug response, and discuss new perspectives on the design of studies that aim to dissect the heterogeneity of this important clinical phenotype.

Learning Objectives:
• To understand the complex nature of the heterogeneity of antipsychotic drug response.
• To learn about new neuroscientific approaches being utilized to dissect the heterogeneity of antispsychotic drug response.

PANEL 5

Assessment and Prediction of Antipsychotic Drug Response
9:00 a.m. - 11:00 a.m.

Defining and Assessing Response in Antipsychotic Clinical Trials

John M. Kane, M.D.
The Zucker Hillside Hospital and Albert Einstein College of Medicine

Measuring response to antipsychotic drug treatment in schizophrenia has enormous practical and heuristic implications. In the process of drug development, metrics need to be used to determine the "efficacy" of a new agent and its relative merits in relationship to available alternatives. Percent improvement over baseline scores is a common metric in analyzing and presenting clinical trial data. However, this measure is highly influenced by baseline scores, making comparison across trials difficult. In addition, common metrics such as 20% improvement reflect minimal rather than optimal improvement. Ultimately, clinicians are interested in producing a degree of improvement such that further changes or manipulations of pharmacologic treatment are no longer necessary in order to enhance symptomatic improvement.

In assessing predictors, either short- or long-term response issues such as adequate dosage, duration, and adherence are critical in drawing meaningful conclusions. There remains considerable debate as to how long an adequate trial should last and what optimum dosing should be for the variety of antipsychotic agents available. In addition, the value of early (e.g. one week) response as a predictor of subsequent response can benefit from further study.

Learning Objectives:
• To provide an overview of response measurement decisions that are involved in everyday clinical practice.
• To suggest strategies for enhancing the measurement of clinical response in research and clinical practice.

PANEL 5

Assessment and Prediction of Antipsychotic Drug Response
9:00 a.m. - 11:00 a.m.

Effects of Schizophrenia Susceptibility Genes on Modulating Cognitive Response to Neuroleptic Agents

Terry E. Goldberg, Ph.D.
The Zucker Hillside Hospital

Several genes have been associated with increased risk for schizophrneia. The val158met SNP in the COMT gene is involved in the degradation of dopamine at the cortical level. Schizophrenic individuals who carry the non-risk met allele demonstrated greater response in cognitive tests of working memory and updating to both typical and atypical neuroleptic drugs. Another gene, DAOA (formerly G72), has been implicated in schizophrenia and bipolar disorder and may have effects at the glycine site of the NMDA receptor. Similar to what was observed for COMT, schizophrenic individuals who carried the non-risk allele demonstrated the greatest improvement in cognition after neuroleptic treatment.

Learning Objectives:
• Participants will recognize the impact of several genes on specific domains in cognition in schizophrenia.
• Participants will understand that it may sometimes be the case that individuals who do not carry the risk allele gene may show the greatest improvement in cognition with neurolptic treatment.

PANEL 5

Assessment and Prediction of Antipsychotic Drug Response
9:00 a.m. - 11:00 a.m.

The Use of Brain Imaging to Predict Antipsychotic Treatment Effects

Robert W. Buchanan, M.D.
Maryland Psychiatric Research Center, University of Maryland School of Medicine

Structural, functional, and chemical imaging techniques may help to delineate the therapeutic and adverse effects of antipsychotic and other medications. Structural magnetic resonance imaging (MRI) has been used to examine the effect of clozapine on caudate volume and to predict treatment response to clozapine. Structural MRI has also been used to examine the long-term effects of second generation versus conventional antipsychotics on brain structure. Positron emission tomography (PET) has been used to define the relationship between dopamine D2 receptor occupancy and positive symptom therapeutic effects, as well as the relationship between occupancy and various side effects. Both PET and functional MRI may be used to delineate the mechanism of action of drugs, through the demonstration of central nervous system activity and where in the brain agents are having their effects. Moreover, magnetic resonance spectroscopy (MRS) and functional imaging techniques may be used to examine the interactions among different neurotransmitter systems and determine whether particular pharmacological approaches are effecting a specific system of interest. Finally, imaging techniques may be used as biomarkers to assist drug development.

Learning Objectives:
• Participants will learn what imaging techniques are used to evaluate antipsychotic treatment effects.
• Participants will learn how imaging techniques may be used to assist drug development.

PANEL 5

Assessment and Prediction of Antipsychotic Drug Response
9:00 a.m. - 11:00 a.m.

Dissecting the Heterogeneity of Schizophrenia: Toward a Molecular Classification of Illness

Anil K. Malhotra, M.D.
The Zucker Hillside Hospital

Gene mapping and candidate gene association studies are now beginning to identify the first convincing susceptibility genes for schizophrenia including dysbindin (DNTBP1, 6p22, {Straub et al. 2002}), neuregulin 1 (NRG1,8p12, {Stefansson et al. 2002}), G72 (13q33, {Chumakov et al. 2002}) regulator of G-protein signaling 4 (RGS4, 1q23; {Chowdari et al. 2002}) and catechol-O-methyltransferase (COMT 22q11-13, {Egan et al. 2001)}. Despite the success of these initial gene-finding efforts, the implications of these results are less clear. The mechanisms by which these genes predispose to illness development is not known, the specific phenotypes associated with risk genotypes remain to be determined, and the relationship of disease genes to treatment response are ongoing lines of investigation.

In this presentation, we will discuss recent data that begin to shed light on the clinical implications of these gene identification efforts. First, we will review new data suggesting that most, but not all, schizophrenia susceptibility genes have modest, yet significant, effects on neurocognitive and neuroimaging parameters commonly impaired in schizophrenia, and data suggesting that gene-targeted treatments may ameliorate some of these deficits in subgroups of patients. Second, we will examine the issue of whether specific risk genotypes can influence the symptomatic presentation of illness, including results indicating that the schizophrenia susceptibility gene, dysbindin, is associated with cognitive impairment and negative symptomatology in schizophrenia. Finally, we will review emerging pharmacogenetic data suggesting that specific genotypic groups may be predisposed toward better treatment response or be at greater risk for drug-induced side effects.

Learning Objectives:
• To understand genetic approaches to the heterogeneity of schizophrenia.
• To examine the ongoing developments in molecular genetic technology and its application to psychiatric disorders.

PANEL 6

Pharmacological Treatment of Borderline Personality Disorder: Recent Findings and Trials Strategies
9:00 a.m. - 11:00 a.m.

Panel Overview

Barbara Stanley, Ph.D.
Columbia University, New York State Psychiatric Institute and City University of New York, John Jay College

Borderline personality disorder (BPD) is a difficult-to-treat disorder with very limited treatment trial data available to guide clinicians. The complex nature of the disorder has made it difficult to conduct medication trials. The NIMH recognized the complexity of conducting trials in BPD by convening a work group to develop strategies. This symposium will describe findings of recent trials and strategies developed both by the work group and each trial for conducting efficacy studies from three separate trials in borderline personality disorder (BPD). These trials are 1) fluoxetine in suicidal and self-injuring individuals with BPD; 2) olanzapine in impulsivity, aggression and depression; and 3) divalproex sodium on impulsive aggression. In addition, the importance of including translational components in trials with BPD will be discussed, and candidates for translational study will be suggested.

Learning Objectives:
• To describe innovative strategies to conduct pharmacological treatment trials in borderline personality disorder.
• To describe recent pharmacological trials findings in borderline personality disorder.

PANEL 6

Pharmacological Treatment of Borderline Personality Disorder: Recent Findings and Trials Strategies
9:00 a.m. - 11:00 a.m.

Fluoxetine and Dialectical Behavior Therapy for Borderline Personality Disorder

Barbara Stanley, Ph.D.
Columbia University, New York State Psychiatric Institute and City University of New York, John Jay College

Borderline personality disorder (BPD) has begun to be recognized as a serious mental illness with significant morbidity and a suicide rate comparable to other serious mental illnesses. Yet few large-scale randomized controlled clinical medication trials in BPD have been conducted. Depression and BPD are frequent co-morbid disorders and, therefore, antidepressant medications are often prescribed for depressed individuals with BPD despite a dearth of efficacy data. We conducted a randomized controlled trial of fluoxetine vs. placebo and Dialectical Behavior Therapy vs. manualized supportive therapy in suicidal and self-injuring individuals with BPD. Results indicate that in the context of supportive therapy, fluoxetine provides additional improvement in depression and suicidality. Implications for further trials will be discussed.

Learning Objectives:
• To describe current fluoxetine results with borderline personality disorder.
• To understand how SSRIs affect suicidal individuals with borderline personality disorder.

PANEL 6

Pharmacological Treatment of Borderline Personality Disorder: Recent Findings and Trials Strategies
9:00 a.m. - 11:00 a.m.

Impulsivity in Medication

Eric Hollander, M.D.
Mount Sinai School of Medicine

The affective instability and impulsive-aggression symptom domain cut across various psychiatric disorders, including borderline personality disorders (BPD), impulse control disorders (IED), and autism. These symptoms, which influence the course of illness and response to treatment, cause substantial impairment in the life of patients with BPD, IED, and autistic disorder. Symptoms include mood instability, self-injury, and aggression, and may be associated with EEG abnormalities in both conditions. Orbitofrontal-limbic circuitry modulated by specific neurotransmitter systems, such as 5HT, glutamate, and GABA, may modulate the expression of both impulsive aggressive behaviors and affective instability. Targeted treatments to modulate key neurotransmitter systems decrease limbic excitability and increase orbitofrontal activity, may reduce symptoms of affective instability and impulsive aggression, and result in substantial improvement in functional ability and more situationally appropriate interactions. Various medication approaches to the management of impulsivity will be discussed.

Learning Objectives:
• Participants will understand a dimensional approach to impulsive-aggression.
• Participants will understand basic mechanisms of impulsive-aggression.
• Participants will receive an overview of the neurobiology and pharmacotherapy of borderline personality disorder, intermittent explosive disorder, and autism.

PANEL 6

Pharmacological Treatment of Borderline Personality Disorder: Recent Findings and Trials Strategies
9:00 a.m. - 11:00 a.m.

Olanzapine for the Treatment of Borderline Personality Disorder: Two 12-Week Randomized Double-Blind Placebo-Controlled Trials

Mary C. Zanarini, Ph.D.
Harvard University

Objective: These are the largest randomized, controlled trials to date evaluating pharmacotherapy for patients with borderline personality disorder (BPD). Two trials examined the safety and efficacy of treatment with olanzapine; the first utilized variable dosing, and the second compared fixed dose ranges.

Methods: Both multi-center, double-blind trials were 12 weeks long, involving patients 18-65 years of age with a DSM-IV-TR diagnosis of BPD. Patients in the variable dose study were randomized to either olanzapine (OLZ2.5-20mg/day; N=155) or placebo (PLA N=159), while those in the dose comparison study were randomized to either 2.5mg/day (OLZ2.5, N=150), 5-10mg/day (OLZ5-10, N=148), or placebo (N=153). The primary efficacy measure was change from baseline to last-observation carried forward endpoint (LOCF) Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) total score. Response was defined as 50% decrease from baseline at any time on the ZAN-BPD total score. Patients were seen in the clinic every two weeks, with a telephone visit between clinic visits.

Results: In the variable dose study, 314 patients were randomized, 71% were female, 86.9% were Caucasian, and the mean age was 31.8 yrs. Approximately half of the OLZ2.5-20 patients had a modal daily dose of 5mg or less, with the most frequent dose being 2.5mg. Baseline ZAN-BPD total scores were indicative of moderate symptoms (OLZ2.5-20: 17.01; PLA: 17.70, p=0.156). ZAN-BPD total scores decreased significantly for both treatment groups, but the magnitude of change did not differ significantly at endpoint (OLZ2.5-20: -6.56; PLA: -6.25, p=.661). Response rates did not differ significantly between groups (OLZ2.5-20: 64.7%; PLA: 53.5%, p=.062), but time to response was significantly shorter for OLZ2.5-20 relative to PLA (p=.022).

In the dose comparison study, 451 patients were randomized, 74% were female, and 65% were Caucasian, and the mean age was 33.0 yrs. Baseline ZAN-BPD total scores were indicative of moderate symptoms (OLZ2.5: 17.01; OLZ5-10: 17.42; PLA: 17.07, p=0.724). Relative to placebo, treatment with OLZ5-10 was associated with significantly greater decreases in ZAN-BPD total score (-8.50 vs -6.79, p=.010), while the OLZ2.5 group approached significance (-8.02 vs -6.79, p=.06). Response rates were significantly higher for OLZ5-10 relative to OLZ2.5 (73.6% vs 60.1%, p=.018) and PLA (73.6% vs 57.8%, p=.006). Time to response was significantly shorter for OLZ5-10 relative to PLA (p=.028).

Treatment-emergent adverse events reported significantly more frequently among olanzapine-treated patients included somnolence, sedation, increased appetite and weight increase. Mean weight change was significantly different for olanzapine- relative to placebo-treated patients (OLZ2.5-20: 2.86kg; PLA: -0.35kg, p<.001; OLZ2.5: 2.09kg; OLZ5-10: 3.17kg; PLA: 0.02kg, p<.001). Rates of treatment-emergent abnormal levels of fasting glucose and fasting lipids did not differ significantly between treatment groups.

Conclusions: In the dose comparison study, treatment with 5-10mg/day of olanzapine was associated with significantly greater improvements in overall symptom severity, whereas the study using variable dosing did not show a significant difference compared to placebo. The types of adverse events observed in the olanzapine treatment groups appeared similar to those observed previously in adult populations.

Learning Objectives:
• To understand the overall effect of olanzapine in borderline patients.
• To understand the effect of olanzapine on certain sectors of borderline psychopathology.
• To understand the side effects of olanzapine in BPD.

PANEL 6

Pharmacological Treatment of Borderline Personality Disorder: Recent Findings and Trials Strategies
9:00 a.m. - 11:00 a.m.

Translational Research in BPD: Incorporation in Treatment Trials

Larry J. Siever, M.D.
Mount Sinai School of Medicine

The last decade has seen an exponential growth in translational research into borderline personality disorder, but, as of yet, rational medication treatment selection for these patients remains problematic. Efficacy in limited controlled trials has been suggested for the SSRIs, anticonvulsants, and atypical neuroleptics. However, there is little guidance as to how to select among these families. Translational studies which suggest that the impulsive aggression of borderline personality disorder may be grounded in reduced prefrontal constraint of limbic reactivity in response to provocation and reduced activity in the serotonergic system associated with both genetic and environmental factors may contribute to this hypofrontality. Reduced activity alleles of the serotonin transporter, reduced binding to transporter, and hypofrontality may predict non-response to SSRIs, while greater severity of impulsivity, bipolar spectrum traits, and limbic hyperreactivity may be predictors of anticonvulsant response. However, there is little in the way of translationally informed treatment trials to definitively and empirically support these hypotheses. A model of altered brain function in relation to the impulsive aggression of borderline personality disorder and implications for how these translational measures may be applied to treatment trials will be discussed.

Learning Objectives:
• To better understand the neurobiology of borderline personality disorder.
• To review the status of current treatment trials in borderline personality disorder.
• To explore how translational measures could be incorporated in treatment trials.
• To appreciate implications for future translational treatment trial studies.

PANEL 7

Medication Management of Mania in Children and Adolescents
9:00 a.m. - 11:30 a.m.

Panel Overview

Benedetto Vitiello, M.D.
National Institute of Mental Health

This panel is intended to provide a research update on the most recent clinical trials testing the effects of mood stabilizers and atypical antipsychotics in childhood mania and to discuss methodological aspects of child bipolar treatment research. Four main topics will be presented. First, the results of an NIMH-funded three-site placebo-controlled trial of lithium and valproate in 154 children and adolescents with bipolar I disorder in the manic or mixed phase will be presented by Drs. Kowatch and Scheffer. Second, Dr. Geller will illustrate the scope, design, methods, and current status of the currently ongoing NIMH-funded Treatment of Early Age Mania (TEAM), a multisite trial of lithium, valproate, and risperidone, alone or in combination, in children with bipolar disorder. Then, Dr. Tohen will present the results of an industry-funded trial of olanzapine in adolescents with bipolar disorder. Finally, Dr. Taylor-Zapata will present a publicly funded project that has been recently launched under the Best Pharmaceuticals for Children Act with the aim to evaluate the pharmacokinetics, efficacy and tolerability of lithium in pediatric bipolar disorder.

Learning Objectives:
- Participants will learn of the most recent evidence of the efficacy and safety of traditional mood stabilizers in children and adolescents with bipolar disorder.
- Participants will learn of the research currently in progress on the effectiveness of pharmacological treatments for pediatric bipolar disorder.
- Participants will learn of methodological aspects of conducting clinical trials in childhood bipolar disorder.

PANEL 7

Medication Management of Mania in Children and Adolescents
9:00 a.m. - 11:30 a.m.

A Randomized, Placebo-Controlled Trial of Divalproex or Lithium in the Treatment of Children and Adolescents with Bipolar I Disorder

Robert A. Kowatch, M.D.
Cincinnati Children's Hospital Medical Center

This is the first large, placebo-controlled trial of lithium or divalproex in children and adolescents with bipolar disorder. One hundred fifty-four outpatient subjects, between the ages of 7-17 years, were randomized in a double-blind to treatment with lithium, divalproex, or placebo in a 2:2:1 ratio. Subjects were diagnosed using the WASH-U-KSADS, and the primary outcome measures were weekly YMRS and CGI-Improvement ratings. The total trial length for each subject was 24 weeks. During the first 8 weeks, subjects were treated with lithium, divalproex, or placebo; in the double-blind and no other psychotropic medications were allowed other than for short-term "rescue." After the first 8-week treatment period, subjects who were responders could continue in the double-blind for another 16 week and have a stimulant medication added if necessary for ADHD symptoms. Subjects who were non-responders during the first 8-week period were re-randomized in the double-blind to another 8 weeks of acute treatment to either lithium or divalproex. We will report on these subjects' demographic and clinical characteristics, as well as their treatment response during this acute and continuation trial.

Learning Objectives:
• Participants will understand the design and methods of this trial.
• Participants will be informed of the results of the acute phase of this trial.
• Participants will be informed of the results of the continuation phase of this trial.

PANEL 7

Medication Management of Mania in Children and Adolescents
9:00 a.m. - 11:30 a.m.

Pediatric Bipolar Collaborative Mood Stabilizer Trial: Safety

Russell E. Scheffer, M.D.
University of Wisconsin, Milwaukee

The Pediatric Bipolar Collaborative Mood Stabilizer Trial was conducted at four academic sites in the United States. This was the first large-scale placebo controlled trial for youth with Bipolar Disorder

Methods: It consisted of an 8-week double-blind, double-dummy comparison of divalproex (DVP), lithium (Li), and placebo (PBO) for the treatment of Bipolar I Disorder in youth ages 7 to 17 years. This was followed by a 6-month extension phase for safety data. Non-responders to the initial assignment were allowed to be reassigned to active treatment (DVP or Li). Side-effects were ascertained using the Side-Effects for Children and Adolescents (SEFCA) at baseline and at each study visit throughout the trial.

Results: Overall, few serious adverse events were reported. Less than 10% of subjects discontinued the trial secondary to side-effects.

Discussion: DVP and Li were well tolerated with minimal drop-outs due to adverse drug reactions. DVP and Li were safe for acute and intermediate term (6 month) use in youth with Bipolar I Disorder.

Conclusions: Divalproex and lithium were well tolerated in both the acute trial and 6-month extension.

Learning Objectives:
• To understand the differences in adverse events reported with divalproex and lithium.
• To understand the drop out rate due to divalproex, lithium, and placebo.
• To understand mediators and moderators of response to divalproex, lithium, and placebo.

PANEL 7

Medication Management of Mania in Children and Adolescents
9:00 a.m. - 11:30 a.m.

Treatment of Early Age Mania (TEAM) Multisite Study

Barbara Geller, M.D.
Washington University, St. Louis

Separate study of treatment for child versus adult BP-I (manic or mixed phase) was deemed necessary based on age specific differences in phenotypic presentation, longitudinal course, and familial aggregation. Specifically, children present with very long episode duration, ultradian cycling patterns during episodes, high rates of comorbid ADHD and ODD, and lower rates of panic and substance use disorders (the latter likely based on young age). On natural history follow-up, there are long times to recovery, short times to relapse, and predominant manic mood. Familial aggregation is 7-8 times higher among first-degree relatives of child BP-I than comparable studies of adult BP-I. Given these differences, and the well-known different actions of various other agents (e.g., tricyclic antidepressants; ketamine) in child vs adult samples, paradigms specific to child BP-I were developed. TEAM is a five data collection site, one coordinating site, study that is now in its third of six years. Due to the novelty and cost of this design, NIMH requested that TEAM begin as a two-year pilot, with the proviso that if the pilot demonstrated feasibility, the investigators would be encouraged to apply for an additional four years of funding to complete the study. TEAM plans to enter 540 subjects (231 were enrolled as of March 15, 2006), aged 6-15 years old with BP-I (mixed or manic phase) and stratified prior to randomization by mixed, cycling, or psychotic status. Regarding treatment, two of the more pressing issues have been (1) which class of drug to use first (lithium, valproate, atypical neuroleptics) and (2) which drug to add-on or switch to if the first drug fails. To investigate these research questions, the TEAM project was initiated as a complex, multi-site, multi-strata, equipoise stratification, adaptive strategy design. In this paradigm, subjects are randomized within three strata that include Stratum One for those on no study medications at baseline or by history. Stratum Two is an add-on strategy for those who are partial responders to one study drug at baseline. Stratum Three is a cross-taper strategy for those who have failed one study medication at baseline. Also, subjects who are partial or poor responders in Stratum One are re-randomized to the other two strata. This controlled, but non-blinded, study randomizes subjects within strata, using the stratifiers noted above, to lithium, valproate, or risperidone. Because it is non-blind, every baseline diagnostic rating (WASH-U-KSADS) is videotaped in its entirety and re-rated by blinded research clinicians at the coordinating site. In addition, all end-of-study ratings are by research clinicians who are blinded to earlier information, including study drug. Rationale for the design and choice of drugs will be discussed.

Learning Objectives:
• To understand the phenotypic, natural history, and familial aggregation differences between child and adult BP-I.
• To gain knowledge of a complex, multistrata, adaptive strategy design.
• To understand the rationale for studying lithium, valproate, and risperidone for child BP-I.

PANEL 7

Medication Management of Mania in Children and Adolescents
9:00 a.m. - 11:30 a.m.

Olanzapine vs. Placebo in Adolescents with Bipolar Mania

Mauricio F. Tohen, M.D.
Eli Lilly and Company

In this 3-week, multicenter, randomized, double-blind, parallel trial, patients 13-17 years of age with a diagnosis of bipolar disorder manic or mixed received either olanzapine (2.5-20 mg/day; N=107) or placebo (N=54). The primary efficacy analysis was mean change from baseline to endpoint in Young Mania Rating Scale (YMRS) total score. Additional efficacy analyses included rates of response (=50% decrease in YMRS total score and CGI-BP Severity of Mania score =3) and remission (YMRS total <12 and CGI-BP Severity of Mania score =3), time to response and remission, and mean changes from baseline to endpoint on the Clinical Global Impression Scale (CGI-BP overall, mania and depression severity), Children's Depression Rating Scale-Revised (CDRS-R), Overt Aggression Scale (OAS), and Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHDRS).

Significantly greater baseline-to-endpoint reductions in YMRS total score were observed for olanzapine-treated relative to placebo-treated patients (-17.7 vs -10.0, p<.001; Effect Size, 0.84). A greater proportion of olanzapine-treated patients met response and remission criteria (44.8% vs 18.5%; p=.002 and 35.2% vs 11.1%; p=.001, respectively) and reached those criteria significantly more rapidly (p=.003 and p=.002, respectively) relative to those who received placebo. Significantly greater improvements with olanzapine treatment were also observed relative to placebo on the CGI-BP (overall and mania severity)(-1.6 vs -1.0; p<.001 and -1.7vs-1.1; p<.001, respectively), ADHDRS (-11.4 vs -7.4; p=.048), and OAS (-3.6 vs -1.9; p<.001) scales.

Somnolence, sedation, increased appetite, and weight gain were treatment-emergent adverse events reported significantly more frequently among patients in the olanzapine-treatment group. The incidence of treatment-emergent weight gain = 7% (41.9% vs 1.9%; p<.001), and hyperprolactinemia were significantly greater for olanzapine-treated relative to placebo-treated patients. The incidence of treatment-emergent abnormal levels of glucose, cholesterol, triglycerides, or uric acid did not differ significantly between treatment groups.

Olanzapine was effective in the treatment of adolescents with bipolar mania. The types of adverse events appeared to be similar to those in adults, but may have differed in magnitude.

Learning Objectives:
• To determine if olazapine is effective in the treatment of bipolar mania in adolescents.
• To determine if olanzapine is safe in adolescents with bipolar mania.

PANEL 7

Medication Management of Mania in Children and Adolescents
9:00 a.m. - 11:30 a.m.

Lithium for the Treatment of Pediatric Bipolar Disorder - NIH Sponsored Protocol

Perdita Taylor-Zapata, M.D.
National Institute of Child Health and Human Development

The National Institute of Child Health (NICHD) at the NIH is sponsoring a clinical trial that will assess the pharmacokinetics, efficacy, and safety of lithium in children and adolescents with bipolar disorder. Lithium was identified as a drug that needed further studies in pediatrics under the Best Pharmaceuticals for Children Act (BPCA). BPCA directs the Secretary of the Department of Health and Human Services, acting through the Director of the NIH and in consultation with the Commissioner of the FDA and experts in pediatrics and pediatric research, to develop and prioritize a list of "off-patent" drugs for which pediatric studies are needed. The studies or trials of pediatric therapeutics under the auspices of BPCA will be through <u>contracts</u> and will address inadequate or absent pediatric safety, efficacy, and dosing information in drug labels.

BPCA: The Process
- NIH develops annually, in collaboration with FDA, experts, parents, and others, an updated list of **off-patent** therapies which *"most urgently"* require study in pediatric populations.
- NICHD established a process to study off-patent drugs from a priority list that is developed annually
  - NICHD organizes study design team with FDA & relevant institutes
  - Funding for BPCA at NIH is distributed among many institutes (~25% to NICHD)
  - NICHD has primary responsibility; organization, **contracting**, monitoring, IND development, collecting data for potential label modification, drafting label modifications for specific ages and indications

There is a distinct difference between a grant and a contract. This will be discussed during the presentation. Also, the entire process of studying off-patent drugs and conducting these studies under a contract will also be discussed.

Lithium Background
- Listed as a drug for priority study under BPCA in 2004
- Literature review done on availability of PK/efficacy data on the use of lithium in pediatrics. Nine studies were identified: 2 RCT, 2 non-RCT trials, 5 case reports or series.
- 1 large double blinded trial was identified:
  - Pediatric Bipolar Collaborative Mood Stabilizer Trial, coordinating PI Dr. Robert Kowatch, Cincinnati, NIMH sponsored R01.

BPCA Lithium Protocols
- The lithium project was awarded to Case Western Reserve University under the leadership of Dr. Robert Findling.
- Scope of Project
  - a pharmacokinetic study that will evaluate different sequences of titrations to reach a maximum tolerated dose (the results of this study will be used to select doses for the subsequent efficacy studies);
  - a randomized, double-blind, parallel group, placebo-controlled acute trial that will last a minimum of 6 weeks and will have adequate statistical power to detect a meaningful difference between lithium and placebo; and
  - a long-term safety study, of no less than 6 months drug exposure, to monitor for adverse events.

Learning Objectives:
- To educate the audience on BPCA and the processes involved in this legislation.
- To inform the audience of the upcoming NICHD-sponsored trial of Lithium in Pediatric Bipolar Disorder.

NIMH PROGRAM SESSION

SBIR/STTR Program at NIMH
11:15 a.m. - 12:15 p.m.

SBIR/STTR Program at NIMH: Process and Priorities

Enid Light, Ph.D.
National Institute of Mental Health

Margaret Grabb, Ph.D.
National Institute of Health

This workshop will provide information about the NIMH SBIR/STTR program. The following areas will be covered: (1) An overview of the SBIR/STTR program; (2) qualifications and application procedures (description of the unique aspects of the SBIR/STTR program and application process); (3) review of SBIR program portfolio and priorities for the NIMH Divisions; (4) how to develop a competitive SBIR/STTR application; and (5) small group technical assistance break-out session.

Learning Objectives:
• Understanding of the unique aspects of the SBIR/STTR application process.
• Knowledge of NIMH priorities for the SBIR program.
• Practical knowledge and skills for submitting and revising an application.

NIMH UPDATE SESSION

NIMH Update
11:15 a.m. - 12:15 p.m.

Patient Reported Outcomes: Can PROMIS Deliver What the FDA Wants?

William T. Riley, Ph.D.
National Institute of Mental Health

PROMIS (Patient Reported Outcomes Measurement Information System) is an NIH Roadmap Initiative to develop a publicly available, adaptable, and sustainable system to improve outcome assessment of patient reported symptoms, functional capabilities, and health-related quality of life for a wide range of chronic diseases. PROMIS utilizes Item Response Theory (IRT) and Computer Adaptive Testing (CAT) to produce highly reliable and efficient assessments of patient-reported domains such as physical functioning, pain, fatigue, emotional distress, and social role participation. This session will present the progress on PROMIS during the first two years of the five year project, including the development of domain structure, item generation, qualitative item review, and the initiation of item calibration testing with over 10,000 respondents. This session will also describe the proposed final product from this effort and its potential applications to clinical trials research. PROMIS will also be discussed in the context of the recent FDA draft guidance on patient reported outcomes measures and the degree to which PROMIS conforms to this draft guidance.

Learning Objectives:
• To obtain a better understanding of the PROMIS initiative and its applicability to clinical trials research.
• To obtain a better understanding of the application of Item Response Theory and Computer Adaptive Testing to patient reported outcome measurement.
• To obtain a better understanding of FDA draft guidance on patient reported outcomes and the degree to which PROMIS conforms to this draft guidance.

PANEL 8

New Targets in Geriatric Psychopharmacology: Expanding Opportunities for Research
2:00 p.m. - 4:00 p.m.

Panel Overview

George T. Niederehe, Ph.D.
National Institute of Mental Health

Older adults are often underrepresented in clinical trials research. Given the advancing age of the population and the polypharmacy often seen in the elderly, more work needs to be done examining both efficacy and effectiveness of psychotropic medications in older adults. In addition, new advances in clinical neuroscience have pushed for the identification of biomarkers and correlates of treatment response variability. Using large-scale clinical trials as platforms, investigators are pursuing a number of hypotheses using contemporary molecular and neuroimaging approaches. This symposium will highlight novel targets for trials and other treatments that may improve participation and response for older adults with psychiatric disorders. Topics will include 1) pharmacotherapy of elders with psychotic symptoms and depression, 2) improving adherence to medical treatments in clinical trials, 3) neuroimaging methods of treatment response, and 4) neuropsychiatric manifestations seen in Parkinson's disease. Experts in the fields of clinical pharmacotherapy and neuroimaging in late-life neuropsychiatric disorders will highlight the role of translational research and the use of these techniques for the development and advancement of clinical practice.

Learning Objectives:
• Understand issues around treatment of elders with psychotic depression.
• Discuss optimal ways to improve adherence to treatment in clinical trials.
• Examine possible biomarkers of late-life neuropsychiatric disease to improve treatment development.

PANEL 8

New Targets in Geriatric Psychopharmacology: Expanding Opportunities for Research
2:00 p.m. - 4:00 p.m.

Improving Adherence to Antidepressant Treatment: The Importance of Patient Beliefs

Charlotte Brown, Ph.D.
University of Pittsburgh School of Medicine

Despite the availability of effective treatments for depression, patient adherence to depression-specific treatment is unacceptably low, with rates of non-adherence often as high as 60%. The present study focuses on adherence as a health behavior that is determined in part by depressed patients' understanding of the illness, beliefs about the impact of depression, and beliefs about depression treatment. Primary care patients' illness models for depression and self-initiated strategies for coping with depression will be described. In addition, age-related differences in the course of antidepressant adherence will be described in patients age 18 to 54 vs. patients age 55+. Multivariate models will be presented which examine the association between illness models for depression and beliefs about medication and patients' adherence (as measured by electronic monitoring caps) to antidepressant medication during acute phase treatment. Implications for interventions to improve adherence to antidepressant medication in primary care settings will be discussed.

Learning Objectives:
• Understand age-related differences in rates of antidepressant adherence in depressed primary care patients.
• Understand the association between beliefs about depression and its treatment and adherence to antidepressant medication.
• Identify modifiable factors that can be the target of brief interventions to improve adherence to antidepressant medication.

PANEL 8

New Targets in Geriatric Psychopharmacology: Expanding Opportunities for Research
2:00 p.m. - 4:00 p.m.

Parkinson's Disease as a Model for the Neural Substrate of Psychiatric Diseases

Daniel Weintraub, M.D.
University of Pennsylvania

Parkinson's disease (PD) is better characterized as a neuropsychiatric disease than a neurological disorder. Disorders that occur at a high frequency include depression, anxiety, psychosis, cognitive impairment/dementia, and disorders of sleep and wakefulness. Other increasingly recognized psychiatric disturbances include disorders of impulse control and emotional expression. There is mounting evidence that both the neurobiological changes that occur in PD (e.g., nigrostriatal degeneration, overall reductions in monoamine levels, disruptions in cortical-striatal-thalamic-frontal cortex circuitry) and the administration of dopamine replacement therapies or other treatments (e.g., electrical stimulation of subcortical structures) can play a role in the occurrence of these psychiatric disorders. Greater understanding of the specific roles that neurobiological changes and various treatments play in the occurrence of psychiatric disorders in PD may also help inform our understanding of the etiology of the same disorders in non-PD patients and potentially lead to new therapeutic interventions.

Learning Objectives:
• To understand the broad range and high frequency of neuropsychiatric disorders that occurs in PD.
• To understand how both the neurobiological changes and treatments used in PD may be relevant to our understanding and treatment of psychiatric disorders in general.

PANEL 8

New Targets in Geriatric Psychopharmacology: Expanding Opportunities for Research
2:00 p.m. - 4:00 p.m.

Neuroimaging Predictors of Treatment Response in Late-Life Depression

Faith M. Gunning-Dixon, Ph.D.
Weill Medical College of Cornell University

Geriatric depression consists of complex and heterogeneous behaviors unlikely to be caused by a single brain lesion. However, there is mounting evidence from neuroimaging studies that abnormalities in frontostriatal-limbic networks often are present in late-life depression. Associations between neuroimaging indices and the clinical presentation, course, and treatment response of geriatric depression can further elucidate the role of these cerebral network abnormalities in the pathophysiology of geriatric depression and the mechanisms of treatment response. This talk will present recent data from multiple neuroimaging techniques regarding frontostriatal-limbic abnormalities that predict response to pharmacologic treatment in late-life depression.

Learning Objectives:
• Participants will become familiar with the potential role of frontostriatal-limbic dysfunction in producing mood disturbances.
• Participants will understand the neuroimaging evidence for the presence of frontostriatal-limbic abnormalities in late-life depression.
• Participants will understand recent neuroimaging evidence for biomarkers of treatment response variability in late-life depression.

PANEL 8

New Targets in Geriatric Psychopharmacology: Expanding Opportunities for Research
2:00 p.m. - 4:00 p.m.

Diagnosis and Treatment of Psychosis in Geriatric Major Depression

Barnett S. Meyers, M.D.
Weill Medical College of Cornell University

Late-life psychotic major depression is associated with poor outcomes, including a poorer response to acute pharmacotherapy, a greater frequency of relapses, and greater mortality than occurs in nondelusional geriatric depression. The design of the NIMH Collaborative Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) is described and design choices are reported. Recruitment into STOP-PD is stratified by age >60 on a 1:1 basis to determine age effects on clinical factors and treatment response. The high frequency of suicidal ideation and recent suicide attempts among the first 180 study subjects are reported, including associations between older age and these phenomena. Complexities of identifying delusions associated with major depression are discussed, including research methods for assessing delusional features. The clinical features of geriatric patients with delusional major depression are compared to those in younger adult subjects. Preliminary data on the effects of older age on the tolerability of study treatments are reported.

Learning Objectives:
• Participants will learn methods for recognizing delusions among elderly patients with major depression.
• Participants will the learn how the characteristics of delusional major depression in later life compare to these characteristics in young adults.
• Participants will learn about the complexities of conducting a randomized controlled trial of geriatric major depression associated with psychosis.
• Participants will become aware of relationships between geriatric delusional depression and suicide.

PANEL 9

Pharmacological Treatment of ADHD in Substance-Abusing Adolescents and Adults: New Findings, Research Directions, and Clinical Implications
2:00 p.m. - 4:00 p.m.

Panel Overview

David S. Liu, M.D.
National Institute on Drug Abuse

Timothy E. Wilens, M.D.
Massachusetts General Hospital

In both adolescents and adults, ADHD and substance use disorders (SUD) co-occur at rates greater than expected by chance. Given that ADHD-SUD comorbidity is associated with a poorer SUD prognosis, delineating the proper treatment of these patients is of great public health concern. Although stimulant and nonstimulant medications are the cornerstone of the treatment of ADHD, it remains unclear whether and how these medications should be used in substance-abusing patients with ADHD.

This panel will present different methodologies and discuss pharmacological outcomes from a growing body of evidence that sheds light on this clinical dilemma, as well as ongoing research efforts in this area. Dr. Wilens will briefly review the relevant literature, and he and Dr. Levin will discuss in detail several placebo-controlled, randomized clinical trials that have directly addressed the questions of safety and efficacy examined in this session: a trial of methylphenidate (MPH) and bupropion for methadone-maintained adults with ADHD; a trial of MPH for adults with ADHD and cocaine dependence; and a multi-site trial of atomoxetine for adults with ADHD and alcohol abuse or dependence. Dr. Winhusen will present a laboratory-based drug-interaction study of cocaine and MPH completed in active cocaine users. Finally, Dr. Somoza and Dr. Winhusen will discuss the rationale, design, and methodological challenges of two multi-site, placebo-controlled randomized clinical trials that are currently being conducted in the NIDA Clinical Trials Network: a trial of OROS MPH for adult smokers with ADHD, and a trial of OROS MPH for substance-abusing adolescents with ADHD.

Learning Objectives:
• Understand the current evidence regarding the safety of pharmacological treatment for ADHD in substance-abusing adolescents and adults.
• Understand the current evidence regarding the efficacy of pharmacological treatment for ADHD on ADHD and on SUD in substance-abusing adolescents and adults with ADHD.
• Understand the methodological challenges encountered in conducting clinical studies of these questions in adolescents and adults comorbid with ADHD plus SUD.

PANEL 9

Pharmacological Treatment of ADHD in Substance-Abusing Adolescents and Adults: New Findings, Research Directions, and Clinical Implications
2:00 p.m. - 4:00 p.m.

Atomoxetine Treatment of Adults with ADHD and Comorbid Alcohol Abuse

Timothy E. Wilens, M.D.
Massachusetts General Hospital

The efficacy of atomoxetine (ATX) as a treatment for adults with ADHD has been shown to be superior to placebo in the treatment of ADHD. However, subjects with current substance-use disorders were excluded from those trials. The primary objective of this recently completed trial, from which data analyses are underway, is to test the hypothesis that treatment with ATX in subjects with ADHD and comorbid alcohol use disorder is 1) superior to placebo in reducing symptoms of ADHD and 2) superior to placebo in the prevention of relapse of alcohol abuse.

After an initial evaluation, recently abstinent adult subjects (from 4-30 days abstinent; N=147) were randomly assigned to receive either ATX (25-100 mg daily) or placebo for a period of approximately 12 weeks, during which time they were seen weekly. ADHD symptoms were measured using the Adult ADHD Investigator Symptom Rating Scale (AISRS).

The Timeline Followback method, in which the subjects' daily drinking is assessed via use of a calendar that covers a specific time period, was employed to measure alcohol use. Time to relapse of alcohol abuse was determined by the number of days from first dose of ATX to first occurrence of relapse.

An update on the progress of the trial, methodological issues, and background on the issue of the comorbidity of ADHD and substance abuse will be presented.

Learning Objectives:
• Understand issues around alcohol use and ADHD.
• Understand study methodology of adults with ADHD and alcohol abuse.
• Understand patient flow through multisite study treating ADHD in alcohol abusers with ADHD.

PANEL 9

Pharmacological Treatment of ADHD in Substance-Abusing Adolescents and Adults: New Findings, Research Directions, and Clinical Implications
2:00 p.m. - 4:00 p.m.

Attention Deficit Hyperactivity Disorder in Substance Abuse

Frances R. Levin, M.D.
New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University

ADHD is overrepresented in substance-abusing populations and has been associated with poorer substance abuse treatment outcome. To date, there are few randomized, controlled trials to assess whether treatment targeting the ADHD symptoms improves both the ADHD symptoms and substance use in actively using substance abusers. Two recently completed double-blind, placebo-controlled clinical trials will be presented. In one trial, 98 methadone-maintained individuals were randomized to either sustained-release methylphenidate (40 mg/day twice a day), sustained-release bupropion (200 mg twice a day) or to placebo. Using standard outcome measures, there was no advantage of active medication in treating ADHD symptoms compared to placebo. Further, among those with active cocaine use (n=52), there was no reduction in cocaine use. In the other trial, 106 cocaine-dependent individuals were randomized to sustained-release methylphenidate (60 mg/day in twice a day dosing) or placebo. Similar to the study conducted in methadone-maintained patients, sustained-release methylphenidate was not superior to placebo in improving ADHD symptoms using standard outcome measures. However, using a semi-structured clinical interview, the Targeted Adult Attention Deficit Disorders Scale (TAADDS), there was a trend for individuals receiving MPH to have a greater reduction in ADHD symptoms over time compared to those receiving placebo. ADHD treatment responders, as determined by the TAADDS, who received MPH showed a reduction in cocaine use over time, while those receiving placebo did not. For non-treatment responders, there was no improvement in cocaine use over time. There are various potential reasons why the therapeutic benefit of active medications commonly used to treat ADHD did not show superiority over placebo in treating ADHD symptoms. These include high placebo response rates, difficulty assessing functional improvement, difficulty perceiving improvement due to active ongoing substance use, less responsiveness to medication, inadequate dosing or absorption of the sustained-release MPH preparation, or poor compliance. Further, it may be that MPH exerts a direct agonist effect and helps reduce cocaine use only if there is a reduction in ADHD symptoms as well. Further avenues of research will be discussed.

Learning Objectives:
• Participants will learn about ADHD substance abuse treatment outcome.
• Participants will learn about methadone, methylphenidate, bupropion.

PANEL 9

Pharmacological Treatment of ADHD in Substance-Abusing Adolescents and Adults: New Findings, Research Directions, and Clinical Implications
2:00 p.m. - 4:00 p.m.

A Pilot Study of Osmotic-Release Methylphenidate (OROS-MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD)

Eugene C. Somoza, M.D., Ph.D.
Cincinnati Veteran Affairs Medical Center, University of Cincinnati College of Medicine

The fact that individuals with ADHD have a significantly higher prevalence of smoking and have greater difficulty quitting was the rationale for initiating this study. The primary objective is to evaluate whether long-acting methylphenidate (OROS-MPH), relative to placebo, increases the effectiveness of standard smoking treatment (i.e., nicotine patch and individual smoking cessation counseling) in obtaining prolonged abstinence for smokers with adult ADHD. Secondary objectives include: 1) evaluating the efficacy of OROS-MPH, relative to placebo, in treating ADHD in smokers with ADHD; 2) evaluating the safety of using OROS-MPH in the treatment of smokers with ADHD; 3) determining the effects of OROS-MPH combined with individual smoking cessation counseling, compared to placebo combined with individual smoking cessation counseling, on smoking behavior. This is a randomized, intent-to-treat, parallel, two-group study comparing the efficacy of OROS-MPH vs. placebo in the treatment of smokers meeting DSM-IV criteria for ADHD. The study consists of two primary phases: the OROS-MPH/Placebo Stabilization phase, and the OROS-MPH/Placebo with Standard Smoking Treatment phase. A total of 252 participants will be recruited from six sites. The design of the study, as well as the advantages and challenges of implementing it within the NIDA Clinical Trials Network (CTN), will be discussed. Final study data will not be available for the presentation, but some screening data will be discussed.

Learning Objectives:
• Participants will gain a basic understanding of the prevalence and consequences of ADHD, smoking, and the interactions between these two very common disorders.
• Participants will become aware of the difficulties of treating these disorders when they occur together.
• Participants will appreciate the rationale, study design, and objectives of this clinical trial.
• Participants will learn how to organize clinical trials to be performed within the NIDA Clinical Trials Network.

PANEL 9

Pharmacological Treatment of ADHD in Substance-Abusing Adolescents and Adults: New Findings, Research Directions, and Clinical Implications
2:00 p.m. - 4:00 p.m.

Methylphenidate and Cocaine: A Placebo-Controlled Drug Interaction Study

Theresa Winhusen, Ph.D.
Cincinnati Veteran Affairs Medical Center, University of Cincinnati College of Medicine

Up to 30 percent of cocaine-addicted individuals may meet diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Methylphenidate (MPH) is a highly effective and commonly used treatment for ADHD but, like cocaine, is a cardiovascular and central nervous system stimulant with the potential to cause toxicity at high doses. The present study was undertaken to investigate the likelihood of a toxic reaction in individuals who use cocaine while concurrently taking MPH. Seven non-treatment-seeking cocaine-dependent individuals completed this placebo-controlled, crossover study with two factors: medication (placebo, 60 mg MPH, 90 mg MPH) and infusion (saline, 20 mg cocaine, 40 mg cocaine). Physiological measures included vital signs, adverse events, and electrocardiogram. Subjective response was measured with visual analog scale (VAS) ratings of craving and drug effect. Cocaine pharmacokinetic parameters were calculated for each participant at each drug combination, using a non-compartmental model. MPH was well tolerated, did not have a clinically significant impact on cocaine's physiological effects, and decreased some of the positive subjective effects of cocaine. MPH did not significantly alter the pharmacokinetics of cocaine. The study results suggest that MPH at the doses studied can likely be used safely in an outpatient setting with active cocaine users.

Learning Objectives:
- Participants will understand the potential safety issues involved in treating ADHD with methylphenidate in patients who are concurrently using cocaine.
- Participants will be able to describe the effects of methylphenidate, up to 90 mg per day, on cocaine's physiological and subjective effects and pharmacokinetics.

PANEL 10

How Can Translational Medicine Change the Success Rate of New Drugs in Psychiatry?
2:00 p.m. - 4:00 p.m.

Panel Overview

William Z. Potter, M.D., Ph.D.
Merck and Company

Gerard R. Dawson, Ph.D.
P1vital Ltd.

Today, the principal cause of failure in clinical development is lack of efficacy and safety (accounting for approximately 30% and 20%, respectively, of all failures). This is a particular problem in CNS drug development, which has a lower than average chance of success due to the poor translation from pre-clinical models to clinical response. Experimental or translational medicine (defined as the "Investigation undertaken in human beings to identify mechanisms of pathophysiology or disease, or to test the validity and importance of new discoveries or treatments, relating where appropriate to model systems") aims to address this issue and currently has a very high priority in both academic and industrial arenas.

Preclinically, both academia and industry have contributed to a large increase in fundamental knowledge, new experimental techniques, and, indeed, whole new classes of candidate compounds for the treatment of psychiatric disorders. However, clinical translation of these findings directly to benefit patients has so far been very limited and almost all of the medicines we think of as new—the atypical antipsychotics or the SSRIs, for example—were conceived as refinements of classical treatments. The failure, so far, to translate the innovations of molecular biology to the clinic have been disappointing. For example, preclinical and early clinical studies suggested that NK-1 antagonists would be effective antidepressants, but subsequent large Phase III studies were negative. Unfortunately, placebo controlled trials are difficult to conduct in patients with the type and degree of depression that most requires pharmacologic intervention. What remains are populations for study in which placebo response rates are high, thereby confounding detection of positive treatment effects. Attempts to compensate for poor signal detection by increasing sample size has often led only to very expensive failed trials. Thus there is a growing gap between the preclinical portfolio and willingness to invest in such large-scale clinical studies.

Despite the very large existing global market for CNS drugs, the spiraling costs of drug development (including lost opportunity costs) are beginning to discourage investment in this therapeutic area. Even for "me too/me better" drugs, the average cost of development is estimated to be about $900 million or more. In the absence of any clear successes, it is impossible to calculate the costs of development for truly novel CNS drugs, a fact which can have a chilling effect on those who must decide on whether to risk the unknown. It is therefore important to understand why is it more difficult to discover and develop drugs for CNS disorders and why the success rate is not improving. Both the lack of translation from promising preclinical data to clinical efficacy and the rising cost of drug development have led to re-evaluation of the clinical approach to evaluating novel compounds in humans. The proposed workshop would address whether we can harness and exploit the strong clinical science base to fill this gap by generating translational data for new compounds, which would be highly predictive of subsequent clinical utility. The approach will be illustrated by focusing on the area of anxiety and depression where new research using small groups of human volunteers aims to provide an early and cost effective method of determining the efficacy of novel compounds.

The workshop is co-chaired by Dr. Gerard Dawson (U.K.) and Dr. Bill Potter (U.S.). Speakers include Dr. Gerry Dawson on human experimental models of GAD and depression being developed in the United Kingdom and France, Prof. Guy Goodwin (U.K.) on elucidating the psychological trait constructs modulated by antidepressant drugs, Dr. Christian Grillon (U.S.) on applications of potentiated startle (an anxiety model which has considerable "face validity" in tracking from animals to humans) and Prof. Murray Stein (U.S.) on performance and other stress-related models relevant to compounds across the anxiety-depression and PTSD spectrum.

Learning Objectives:
• To understand what translational medicine is with regard to the development of novel psychotherapeutic agents.
• To fully appreciate what makes a good translational medicine assay for drug development compared with studying a disease process.
• To elucidate the issues in translating human experimental assays to animal models and vice versa.

PANEL 10

How Can Translational Medicine Change the Success Rate of New Drugs in Psychiatry?
2:00 p.m. - 4:00 p.m.

Translation Models of GAD and Depression — What Are They and We Do We Need Them?

Gerard R. Dawson, Ph.D.
P1vital Ltd.

GAD is a relatively under researched condition, and much still needs to be learned about its causes and how the condition might be treated. In common with other psychiatric conditions that are also under-researched, developing a human model of GAD, a "challenge" that reliably reproduces GAD symptoms, will be useful to investigate how GAD symptoms occur, and to test potential medications in healthy volunteers, and in patients. To be effective, any potential model needs to reliably reproduce anxiety in healthy people, and the degree of anxiety provoked should be repeatable and measurable. In addition, the effects of known anxiolytics in the model should mirror those in patients. Animal models of anxiety, such as conditioned emotional response (CER), is one such model that meets these criteria, and human analogues of this model have been developed using healthy human volunteers. Healthy volunteers are by definition not anxious, so any challenge should significantly increase self rating scores of anxiety and other associated symptoms. A possible model of GAD using the inhalation of increased levels of carbon dioxide (7.5% CO_2) for 20 minutes (Bailey et al. 2005) has been developed and validated with benzodiazepines and SSRIs. In healthy volunteers, this challenge induces anxiety and tension, reduces feelings of being relaxed and happy, and increases blood pressure and heart rate. All these effects of CO_2 are significantly different from breathing normal air (the control condition). However, the question still remains: how much do the subjective feelings of anxiety experienced by volunteers in the CO_2 model share a common space with the symptoms of anxiety experienced by GAD patients? In this respect, a model that includes subjects with a underlying anxiety condition, such as the dental phobia model, may be of potential interest. Dental phobia is a widespread problem which prevents patients seeking regular dental care. Up to 15% of the adult population in the United Kingdom are dental phobics who will only accept dental care whilst they are sedated or anaesthetised. Consequently, dental phobia provides a unique model of acute anxiety which can be used to test novel therapeutic agents for anxiety conditions. Developing similar translational models of depression has proved more difficult. Depression is characterised by increased fearfulness, feeling of worthlessness, impaired reward processes and, more recently, increased impulsiveness has been noted as a common symptom. Developing an animal model of this complex condition has long been a challenge to the preclinical research community. More recently, clinical work has focussed on investigating the impaired psychological and cognitive processes characteristic of depression and the common pharmacological fMRI (pfMRI) signal of antidepressant drugs detected. These new approaches have yielded interesting results that have both illuminated potential strategies for increasing our understanding of the depression and new approaches to developing translational models.

Learning Objectives:
• To understand the role of translational medicine in psychiatry.
• To understand the challenges of developing an experimental medicine model of GAD.
• To understand the challenges of developing an experimental medicine of depression.

PANEL 10

How Can Translational Medicine Change the Success Rate of New Drugs in Psychiatry?
2:00 p.m. - 4:00 p.m.

Integration of Basic and Clinical Studies of Fear and Anxiety

Christian Grillon, Ph.D.
National Institute of Mental Health

Advances in the neurobiology of aversive motivational states have not been accompanied by similar progress in elucidating the pathophysiologic underpinnings of the anxiety disorders and in designing better psychopharmacological treatments for such conditions. Keys to successful translational research are the implementation of experimental models that can be replicated across species, and the development of experiments that closely model clinical phenomena. The cross-species methodologies of fear conditioning and fear-potentiated startle provide important avenues toward this end (Grillon & Baas 2002).

Fear-potentiated startle refers to the increase in startle reactivity during the anticipation of aversive stimuli. In rodents, fear-potentiated startle is mediated by two different structures, the amygdala and the bed nucleus of the stria terminalis (BNST). These two structures are responsible for the functionally distinct aversive states of fear, a phasic response to a clearly identified danger, and anxiety, a more sustained aversive state not clearly linked to a cue (Davis et al 1998). Fear-potentiated startle can also be obtained in humans with experiments analogous to those used in animals. We have proposed that fear-potentiated startle to threat of predictable shock reflects amygdala-mediated phasic fear, whereas threat of unpredictable shock reflects BNST-mediated sustained anxiety (Grillon et al, 2004). This presentation will focus on the pharmacological and clinical validation of procedures in which startle is elicited during threat of predictable and unpredictable aversive stimuli in humans. We will show that the benzodiazepine alprazolam reduces fear-potentiated startle to unpredictable shock, but not to predictable shock, whereas acute treatment with the SSRI citalopram yields opposite effects. We will also present data suggesting that across the spectrum of anxiety disorders, individuals with generalized anxiety show greater sensitivity to shock unpredictability than those with specific phobias, a finding consistent with characterizing anxiety disorders subtypes as primarily anxiety- or fear-related, respectively.

Learning Objectives:
• To understand the psychophysiological approach to anxiety and anxiety disorders.
• To learn about fear-potentiated startle as a translational experimental models of anxiety.

PANEL 10

How Can Translational Medicine Change the Success Rate of New Drugs in Psychiatry?
2:00 p.m. - 4:00 p.m.

Shortcuts to Anxiolytic Drug Development: The Road Ahead

Murray B. Stein, M.D., M.P.H.
University of California, San Diego

No new classes of anxiolytic medications have entered the marketplace in the past two decades, and the current drug development pathway suffers from many costly, time-consuming failures of compounds that enter Phase II/III studies. The FDA has pointed to this "pipeline problem" as a significant challenge to drug development in the 21st century. Among its recommendations is the need to invent new drug development tools to enhance the movement along the "critical path" from Phase I to Phase III.

This presentation will review the use of pharmacological (e.g., yohimbine; doxapram), physiological (e.g., hyperventilation; enriched carbon dioxide inhalation), and more naturalistic stress (e.g., Trier Social Stress Test) challenges that have been proposed to facilitate anxiolytic drug development. This will include a review of the predictive validity of these methods for determining likelihood of anxiolytic drug effects. The use of blood oxygen dependent (BOLD) functional magnetic resonance imaging (fMRI) to probe the activation in amygdala, insula, and medial prefrontal cortex with standard anxiolytic and other psychopharmacological agents will also be discussed. This use of pharmacofMRI to examine drug effects at specific targets within established fear circuits is proposed as among the most promising translational techniques to increase the likelihood of success in moving anxiolytic agents from bench to bedside.

Learning Objectives:
- Review the literature on available pharmacological or physiological "challenges" to elicit anxiety symptoms (e.g., hyperventilation, carbon dioxide, lactate, doxapram, Trier Stress Test, etc.)
- Discuss predictive validity of these models for identifying pharmacologically active (anxiolytic) compounds in early Phase II drug development.
- Discuss alternative models for identifying anxiolytic drugs early in Phase II, with emphasis on pharmacofMRI.

PANEL 10

How Can Translational Medicine Change the Success Rate of New Drugs in Psychiatry?
2:00 p.m. - 4:00 p.m.

How Do Antidepressants Work?

Guy M. Goodwin, M.D., D.Phil.
University of Oxford

There are no established, valid models of depression in man. Pharmaceutical companies have poured significant resources into discovering and developing new treatments for mood disorder, and, on the preclinical side of the translational medicine equation, the combined resources of academia and industry have resulted in a phenomenal increase in fundamental knowledge, new experimental techniques, and, indeed, whole new classes of candidate compounds. However, clinical translation of these findings directly to benefit psychiatric patients has so far been very limited. Placebo controlled trials in depression are difficult to conduct in patients with significant severity of depression, and high placebo response rates confound detection of positive treatment effects. Such trials are also extremely expensive, and promising candidate medicines may founder because of chance effects in very expensive clinical studies.

Our objective is to fill the evident gap between the preclinical portfolio and such large-scale clinical trials by establishing models of depression in man that will be predictive of subsequent clinical utility. We have recently shown that reliable behavioral effects can be obtained from different types of antidepressant upon the detection of emotional expression in faces and the emotional bias in incidental memory in healthy volunteers. In a series of studies, a selective serotonin reuptake inhibitor (SSRI), citalopram, and a selective noradrenaline reuptake inhibitor (NARI), reboxetine, increased positive emotional bias (Harmer et al 2003 Am J Psych 160, 990-2; Psychopharmacology 167: 411-7; Neuropsycho-pharmacology 28(1): 148-152; 2004 Am J Psych. 161, 1256-1263). Thus, these effects would counter prevailing negative emotional biases easily elicited in depression. The effects have also been examined in imaging paradigms using BOLD fMRI (Harmer et al. 2006 Biological Psychiatry - in press). Negative emotional expressions, even when presented subliminally by using backward masking, are associated with an attenuated signal in the amygdala after treatment with a SSRI, and the encoding of positive but not negative words is associated with increased activation in frontal and parietal areas during treatment with a NARI antidepressant. Thus, the experiments are exactly analogous to experiments in normal animals that show emotionally relevant effects. They could contribute to a preclinical portfolio of dose/effect data and the face validity of a novel compound.

Learning Objectives:
• To demonstrate antidepressant effects on emotional processing.
• To demonstrate neural activity underlying antidepressant effects.
• To explore emotional processing bias in clinical groups.
• To propose an experimental medicine approach for depression in man.

Food and Drug Administration Symposium
9:00 a.m. - 12:00 p.m.

New Labeling on the Horizon

Thomas P. Laughren, M.D.
Food and Drug Administration

FDA has published a new physician labeling rule along with a draft guidance for implementing this new rule. The new rule calls for a new "Highlights" section, a table of contents for the full prescribing information, and a reorganization of the full prescribing information. This talk will summarize important features of the new labeling and describe how the conversion to new labeling is expected to be accomplished. FDA's required timetable for implementation will be provided. Other FDA initiatives that are related to this labeling initiative will also be discussed.

Learning Objectives:
• Participants will learn about key features of FDA's new physician labeling rule.
• Participants will learn how conversion to the new labeling requirement will be accomplished.
• Participants will learn about other FDA initiatives that will help in implementation of the new labeling rule.

Food and Drug Administration Symposium
9:00 a.m. - 12:00 p.m.

New Data Regarding Exposure to SSRIs During Pregnancy

Alice Hughes, M.D.
Food and Drug Administration

New data from epidemiological studies have emerged pertaining to non-teratogenic and teratogenic effects of exposure to SSRIs during pregnancy. Prior to September 2005, available evidence had not implicated the SSRIs, collectively or individually, as human teratogens. Two recent studies have indicated an increased risk for overall congenital malformations, and cardiovascular malformations in particular, following exposure to the SSRI paroxetine during early pregnancy. A third study has demonstrated an increased risk for persistent pulmonary hypertension of the newborn (PPHN) following exposure to SSRIs after the 20th week of gestation. This talk will review the new data and discuss the actions that the FDA has taken and plans to take in response.

Learning Objectives:
• Participants will understand the nature and magnitude of the risk for birth defects following exposure to paroxetine during early pregnancy, according to recent studies.
• Participants will understand that SSRIs may increase the risk for persistent pulmonary hypertension of the newborn following exposure in late pregnancy.
• Participants will recognize the limitations of epidemiological data for studying the teratogenic and nonteratogenic effects of SSRIs.
• Participants will become aware of the FDA's recommendations pertaining to the use of SSRIs during pregnancy.

Session I Posters Presented on Tuesday
Session II Posters Presented on Wednesday

All poster presentations are copied verbatim and appear in category listing per day as outlined below:

Poster Session I (Tuesday, June 13, 12:00 p.m. - 2:00 p.m.)

Primary Topic	Poster Number
ADHD	1, 2, 3, 4
Alcohol/Substance Use Disorder	5
Anxiety Disorder (Other than OCD)	6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16
Bipolar Disorder	17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36
Childhood/Adolescent Disorder (Other than ADHD)*	37, 38, 39, 40, 41, 48
Comorbid Mental and Substance Use Disorders	42, 65
Depression	43, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64
Other	73, 80, 92, 93, 94, 96, 97, 98, 99, 100, 101, 102
Psychotic Disorder (Other than Schizophrenia)	66
Schizophrenia	67, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 79, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 103
Women's Mental Health Issues	91, 95

Poster Session II (Wednesday, June 14, 12:00 p.m. - 2:00 p.m.)

Primary Topic	Poster Number
ADHD	1, 2, 3, 4, 5, 6, 7, 8, 9, 10
Alcohol/Substance Use Disorder	11, 12, 13
Bipolar Disorder	14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25
Childhood/Adolescent Disorder (Other than ADHD)*	26, 27, 28, 29, 30, 31
Comorbid Mental and Physical Disorders	32, 33, 34, 35, 37, 38
Dementia or Other Geriatric Disorder*	39, 40
Depression	36, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 63, 64, 65, 66, 67, 68, 69
OCD or Related Disorder	62, 70
Other	71, 72, 73, 74, 75, 76, 77, 78
Schizophrenia	79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 102
Sleep Disorder	97, 98, 99, 100, 101, 103, 104

Session I - 1

Long-Acting Stimulants and Mood Symptoms in Teenagers with ADHD: Parent and Adolescent Perspectives

Mark Stein, Ph.D. [1], David Black, Ph.D. [2], Larry Merkel, Ph.D., M.D. [3], Frances Thorndike, Ph.D. [3], Roger Burket, M.D. [3], Melissa Moore, M.D. [3], Daniel Cox, Ph.D. [3]

[1]University of Illinois, Chicago, [2]Boston University School of Medicine, MA, [3]University of Virginia, Charlottesville

Background: Adolescents with ADHD often display comorbid mood disorders. However, stimulant medication and withdrawal from stimulant medication (i.e. rebound) may also result in mood symptoms such as dysphoria and irritability. It is unclear how common and when these mood symptoms occur in adolescents with ADHD, and if there are differences between the two most commonly prescribed stimulant medications (methylphenidate versus amphetamine).

Objective: We sought to compare the effects of long-acting MPH (Concerta) and MAS (Adderall XR) on irritability and mood symptoms during the day as compared to evenings when the behavioral effects of stimulant medication have typically worn off. Since parent and self-report may differ, both informants were utilized.

Methods: Males (19) and females (17) between ages 16-19 (Mean = 17.8) with ADHD participated in a double-blind crossover study of MAS and MPH. All participants underwent a blinded, 10-day titration before reaching the target dose of 30 mg. MAS or 72 mg. MPH, which they received for 7 days. Then subjects were crossed over to the alternative medication. During the study, an alarm sounded at 6 p.m. and 10 p.m. on a personal digital assistant, signaling participants and their parents to complete severity ratings (0-4) of several mood symptoms.

Results: Irritability/moodiness was much more common than dysphoria or anger, according to both parents and adolescents. During the day when medications were most active, parents reported moderate to severe irritability in 29% of those treated with MAS and 22% of those treated with MPH (ns). During the evening, irritability declined slightly (p = .06). According to adolescent self-report, irritability was also more common than dysphoria or anger, with moderate to severe irritability occurring in 16% of those taking MAS and 17% taking MPH. There were no significant differences between daytime and evening ratings or type of stimulant on adolescent self-report measures.

Conclusions: In a sample of teenagers with ADHD treated with robust doses of long-acting stimulants, moderate to severe irritability occurred in 22-29% and decreased to 17-15% in the evening, according to parent ratings. Dysphoria was less common, occurring in 9% or less. There was little evidence of stimulant rebound or worsening of mood. In fact, parent ratings of irritability indicate slightly less irritability after 6 p.m. for both MPH and MAS.

The conclusions should be tempered by limitations of the study design, which did not include a placebo period, and by modest sample size, which consisted of stimulant responders and excluded individuals with severe psychiatric comorbidity. Due to the relationship between tolerability and compliance, future studies are needed with larger samples to study mood symptoms throughout the day and the relationships with ADHD and ADHD treatments.

Session I - 2

Risperidone Augmentation for Treatment-Resistant Aggression in Attention Deficit/Hyperactivity Disorder

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Background: Atypical antipsychotics are commonly employed in combination with psychostimulant agents for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD), particularly when aggressive behaviors are present. However, there is no scientific database available to guide clinicians regarding efficacy or safety of these combinations. The primary objective of this study is to evaluate the effects of risperidone augmentation for treatment-resistant aggression in children with ADHD.

Methods: Children (7-12 years of age) meeting DSM-IV criteria for ADHD with significant aggressive behaviors were randomized to risperidone or placebo for 4 weeks. All subjects were already in treatment with a constant dose of a psychostimulant agent. The primary efficacy measure was change from baseline in the Children's Aggression Scale-Parent (CAS-P) and Teacher (CAS-T) total scores. Safety was assessed primarily through adverse event monitoring.

Results: Twenty-five subjects participated in the study, with 13 assigned to risperidone treatment and 12 assigned to placebo. Risperidone doses ranged from 0.5 to 2.0 mg/day (mean=1.125 mg/day). Chi Square Analyses: For the CAS-P total score, a significant difference was found (X^2 = 4.30 (1), $p < .05$) with 100% of risperidone subjects improving by more than 30% from baseline to week four, while 23% of placebo subjects changed less than 30%. No other differences were found for the individual subscales.
Repeated Measures Analyses: For the CAS-P and CAS-T, no significant interaction was found between treatment group and time. A change was noted over time for the total score and for all subscales as the scores for both treatment groups decreased from baseline to week four. Adverse events were generally mild in intensity. None of the subjects discontinued treatment because of adverse events. Risperidone produced no changes in Body Mass Index when combined with psychostimulant agents.

Conclusions: Risperidone treatment appears to be a well-tolerated and moderately effective augmenting strategy for treatment-resistant aggression in children with ADHD.

Session I - 3

Stimulant Treatment Prevalence: A Cross-National Comparison

Julie Zito, Ph.D. [1], Daniel Safer, M.D. [2], Joerg Fegert, M.D. [3], Loljke deJong-vandenBerg, Ph.D. [4], Katrin Janhsen, Ph.D. [5], Corrine deVries, Ph.D. [6], Gerd Glaeske, Ph.D. [5], James Gardner, Sc.M. [1]

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Background: Prominent differences in the prevalence of antidepressant and antipsychotic medications have been reported between youth in the United States and Western Europe. Similar comparisons of stimulant prevalence have been few, because until the mid-1990s, these drugs were seldom prescribed in Europe.

Methods: A cross-sectional analysis of year 2000 administrative prescription claims or records from the Netherlands, the United States, the United Kingdom, and Germany was undertaken. The Dutch data represent youths from the northern Netherlands captured in a pharmacy database (n=110,944); The U.S. data are derived from a large Medicaid State program according to the youth's eligibility in a selected group (s-CHIP: n=127,157) that is most comparable to the other groups in terms of socioeconomic and health status. The U.K. data come from a General Practice Research Database (GPRD) (n=177,658). The German data (n=356,520) were derived from a large regional health insurance company. Annual stimulant prevalence for youth under age 20 is defined as the number of youth with one or more prescriptions for a stimulant per 100 youth enrolled during the year 2000. We compared the prevalence (and the 95% confidence limits) data by age group (0-4, 5-9, 10-14, and 15-19) and by gender. Prevalence rate ratios between groups were also calculated.

Results: The major findings were: 1) U.S. prevalence was 2.5, 3.6, and 13 times more common than in their Dutch, German, and U.K. counterparts, respectively. 2) Stimulant prevalence for U.S. youths aged 0-4 was 0.44%, whereas it was 0 in the U.K. and minimal in the Netherlands (0.05%) and in Germany (0.02%). 3) In the United States, the male: female ratio was 3.4:1. Girls were medicated relatively less in Western Europe (M:F ratio ranged from 4.8-9.5:1). 4) In the United States, methylphenidate and amphetamines were prescribed to an equivalent degree (49% vs. 51%), whereas in Western Europe, methylphenidate was the predominant stimulant prescribed (95%-97%).

Conclusions: Major stimulant treatment differences in type of drug, prevalence of use, gender, and age remain between one European country and another and between these countries and the United States.

Source of Funding: None

Session I - 4

Pharmacokinetics of Extended-Release Guanfacine in Children and Adolescents with ADHD

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Background: The nonstimulant guanfacine immediate-release (alpha 2A-adrenoreceptor agonist) has been used off-label for ADHD, but it has a short duration of action. This study evaluated single and multiple oral dose pharmacokinetics of an extended-release formulation of guanfacine (GXR) in children and adolescents diagnosed with ADHD.

Methods: An open-label, dose-escalation study was conducted in children (aged 6-12 years) and adolescents (aged 13-17 years) with ADHD. Subjects received a single 2 mg dose on day 1. On days 9-15, subjects received 2 mg/qd; on days 16-22, 3 mg/qd; and on days 23-29, 4 mg/qd. Vital signs, ECGs, and plasma samples were taken predose on day 1 and at intervals over 24 hours, with repeat schedule on days 14 and 28, and additional assessments on days 2-5, 15, and 29.

Results: GXR pharmacokinetics were linear in children (n=14) and adolescents (n=14), and time to maximum exposure (T_{max}) was nearly identical. Mean plasma concentrations and peak exposure (C_{max}) were higher in children than in adolescents. The area under the concentration-time curve exposure ($AUC_{0-\infty}$) was 65.2±23.88 h•ng/mL in children and 47.3±13.69 h•ng/mL in adolescents, post–single dose. Mean half-life was 14.4±2.39 h in children, and 17.9±5.77 h in adolescents.

Mean±SD	2 mg Single Dose		2 mg Multiple Doses		4 mg Multiple Doses	
	Children	Adolescents	Children	Adolescents	Children	Adolescents
C_{max} (ng/mL)	2.6±1.03	1.7±0.43	4.4±1.66	2.9±0.77	10.1±7.09	7.0±1.53
T_{max} (h)*	4.98	4.96	4.98	4.53	5.02	4.97
AUC_{0-24} (h•ng/mL)	NA	NA	70.0±28.33	48.2±16.06	162.1±115.56	116.7±28.37
CL/F (mL/min) (mL/min/kg)	578±215 19.0±8.08	754±190 13.3±2.85	552±215 15.3±4.11	826±486 14.4±8.34	522±212 14.3±3.70	607±166 10.7±3.11

*Median. NA=not available

No discontinuations occurred due to adverse events (AEs). The most frequent possibly/probably treatment-associated AEs were somnolence, insomnia, headache, and blurred vision. Most were mild to moderate in intensity, with the highest incidence associated with the 4 mg doses. Blood pressure, pulse, and ECG readings were within normal limits.

Conclusions: Plasma concentrations and pharmacokinetic parameters were higher in children than in adolescents, probably due to the higher weight in adolescents. GXR exposure in both groups was approximately twice as high after repeated daily administration of 4 mg than after 2 mg, consistent with the linear pharmacokinetics. GXR was generally well tolerated and safe.

Session I - 5

Is Maternal Methadone Associated with Infant Birth Outcomes?

Debra L. Bogen, M.D. [1], Barbara H. Hanusa, Ph.D., M.S. [2], Wesley C. Barnhart, B.S. [3], Katherine L. Wisner, M.D., M.S. [2]

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Background: Methadone maintenance therapy is the current standard of care for pregnant, opiate-dependent women. In response to data that higher methadone doses are associated with better adherence to treatment programs and improved pregnancy outcomes, women are now prescribed higher methadone doses during pregnancy. However, there needs to be a risk-benefit balance between maternal and infant outcomes. The impact of higher methadone doses on infant outcomes has not been well studied.

Objective: The objective of this study was to examine the association between birth outcomes and maternal methadone dose at delivery.

Methods: We used de-identified data abstracted from medical records for all methadone-exposed mother-infant dyads born at a single hospital from 1999-2004. The birth outcomes evaluated were birth weight, gestational age, small-for-gestational age (SGA), 5-minute APGAR score less than 9, admission to the NICU, and length of stay. A composite poor outcome variable was created that included SGA, NICU admission, and 5 minute APGAR <9. The main predictor was daily methadone dose grouped into 3 levels, low (<60 mg), medium (60-89 mg), and high ($\geq$ 90 mg). Of the 173 women on methadone maintenance therapy during pregnancy, we excluded 26 who also used cocaine during pregnancy, 19 whose charts were missing or unavailable, and 3 whose babies were born before 25 weeks.

Results: Of 117 women, 34% were older than 30 years, 95% were white, 81% received Medicaid, 70% had no more than a high school education, 83% were unmarried, and 78% smoked during pregnancy. The methadone doses at delivery ranged from 13 to 210 mg/day; the mean daily dose was 80mg and the median dose was 75mg. There were no associations between maternal demographic characteristics and methadone dose levels.

Methadone dose was not statistically associated with gestational age < 37 weeks or birth weight < 2500g. Although admission to the NICU, SGA, and 5 minute APGAR score <9 were only associated with methadone dose at borderline significance levels, the composite variable of any poor outcome was (exact test of linear by linear association p=0.02) Infants exposed to higher doses had more poor outcomes. For example, of infants exposed to low dose methadone, 43% had no poor outcomes; compared to 29% exposed to medium dose and 18% exposed to high dose methadone. Infants exposed to high dose ($\geq$ 90mg) had more multiple (2 or 3) poor outcomes (36%) versus infants exposed to low dose (18%). This result was not changed when adjusted for maternal smoking status.

Conclusions: Higher maternal methadone doses are not associated with individual adverse birth outcomes but are associated with increased risk of any adverse birth outcome. This needs to be evaluated in prospective studies.

Session I - 6

Signal Detection Properties of Three Outcome Scales in Clinical Trials in Patients with Generalized Anxiety Disorder

Qin Jiang, B.S., Saeed Ahmed, M.D., Ron Pedersen, M.S., Jeff Musgnung, M.T., Richard Entsuah, Ph.D.

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Objective: Clinical trials in patients with psychiatric disorders typically utilize a number of scales to assess outcome. In this analysis we examined correlations between three outcome scales and their signal detection properties (drug vs placebo) in a generalized anxiety disorder (GAD) clinical trial dataset. The three scales examined are the 14-item Hamilton Rating Scale for Anxiety (HAM-A), the Clinical Global Impression of Severity (CGI-S), and the Clinical Global Impression of Improvement (CGI-I).

Methods: Data from five randomized, double-blind, placebo-controlled venlafaxine extended release studies in adult patients with GAD were pooled and examined individually. For all rating scales, Pearson correlation coefficients were calculated for all patients at each visit and by treatment arm. To evaluate signal detection properties, effect sizes and p-values based on the pooled and individual study data were examined for the three scales.

Results: At pretreatment visits, for the HAM-A and CGI-S, respectively, 1837 and 1831 observations were available, with mean scores of 25.8 and 4.5, and the correlation coefficient (r) between the two scales was .55 (p<.0001). R's at week 1 were .69 (HAM-A/CGI-S), .66 (HAM-A/CGI-I), and .55 (CGI-S/CGI-I); increased each week; and at final visit were .83 (HAM-A/CGI-S), .84 (HAM-A/CGI-I) and .82 (CGI-I/CGI-S). All correlations were highly significant (p<.0001), and were of comparable magnitude in the venlafaxine and placebo groups. Pooled effect sizes (venlafaxine vs placebo) were .37, .41, and .40 for HAM-A, CGI-S, and CGI-I, respectively (week 8 LOCF). Across studies, effect sizes ranged from .21 to .55, .23 to .68, and .26 to .59 for the HAM-A, CGI-S, and CGI-I, respectively; however, as with the pooled data, within studies, they were more consistent across the three outcome measures. All three outcome measure reached statistical significance (p<.05) in four of five studies.

Conclusions: The three scales were consistently correlated in all studies, and the correlations increased during the conduct of the study. Effect sizes based on different scales in the same studies were more similar than effect sizes based on the same scale in different studies. Furthermore, no one scale stood out as having consistently better signal detection properties than the others.

Session I - 7

Generalized Anxiety Disorder (GAD): Can the Hamilton Psychic Anxiety Subscale Be Employed to Measure Primary Drug Response?

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Background: The Hamilton Anxiety Rating Scale (HAM-A) is employed as the "gold standard" for evaluating primary drug response in clinical trials assessing generalized anxiety disorder (GAD) treatment. However, the total HAM-A assesses symptoms that do not match DSM-IV "core" pathology of this disorder. The HAM-A Psychic Anxiety subscale is more closely aligned with "core" GAD symptoms and therefore may provide more concise assessment of drug response.

Objective: Evaluation of the HAM-A Psychic Anxiety subscale as an alternative method for determining drug response in GAD treatment.

Methods: Four double-blind, randomized placebo-controlled trials evaluating the use of paroxetine IR or paroxetine CR in outpatients diagnosed with GAD, were included in these retrospective analyses (studies 637, 641, 642, and 791). These were 8-week studies employing the HAM-A total score change as the prospectively defined primary efficacy measure. Change on the HAM-A Psychic Anxiety subscale was prospectively defined as a secondary efficacy measure. In addition, a HAM-A "GAD subscale" was retrospectively derived from the full HAM-A as a measure of efficacy (items 1, 2, 4, 5, and 7). Endpoint effect sizes and p-values were calculated and presented separately for each study. Mean effect sizes incorporating all four studies were further derived.

Results: These trials included 688 placebo, 727 paroxetine IR, and 163 paroxetine CR patients. Of these, only studies 641 and 642 demonstrated statistical significance in favor of the active drug (paroxetine IR) relative to placebo, using the HAM-A total score as the primary efficacy measure (641: 20mg= p<0.001, 95% C.I. = [-4.6, -1.2]; 40mg= p<0.001, 95% C.I. = [-4.2, -0.9]; 642: p=0.008, 95% C.I. = [-4.0, -0.6]). Using the Psychic Anxiety subscale, all four studies achieved statistical significance for the active drug compared to patients receiving placebo. For the HAM-A "GAD subscale," only study 791 was not statistically significant for active drug (paroxetine CR) relative to placebo (p=0.061). The mean effect sizes combining study results were 0.23, 0.29, and 0.29 for the HAM-A total score, Psychic Anxiety subscale, and HAM-A "GAD subscale", respectively.

Conclusions: HAM-A subscales more closely aligned with DSM criteria (such as the Psychic Anxiety subscale) may offer an alternative more concise method of assessing drug response in the treatment of generalized anxiety disorder.

Session I - 8

Quetiapine Monotherapy in Patients with Generalized Anxiety Disorder

Olga Brawman-Mintzer, M.D. [1], Paul J. Nietert, Ph.D. [2], Moira Rynn, M.D. [3], Karl Rickels, M.D. [3]

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Objective: Atypical antipsychotics have demonstrated potential efficacy as augmenting agents in treatment-resistant generalized anxiety disorder (GAD). [1,2] This double-blind, placebo-controlled trial assessed the efficacy of quetiapine monotherapy in GAD.

Methods: Thirty-eight non-depressed patients with GAD (HAM-A total score >20) were randomized, following a one-week placebo run-in, to quetiapine (25-300 mg/day) or placebo (assessments at Weeks 1, 2, 4, and 6). The primary efficacy variable was change from baseline in HAM-A total score at Week 6. Response ($\geq$50% reduction in HAM-A total score) and remission (HAM-A total score $\leq$7) rates were also assessed. Safety assessments included AIMS, SAS, BAS, and monitoring of adverse events (AEs).

Results: Twelve of 19 quetiapine and 16 of 19 placebo patients completed treatment. There was no significant difference between quetiapine (mean endpoint dose 125 mg/day; median dose 100 mg/day) and placebo in HAM-A total or psychic subscale scores at Week 6. However, observed cases analyses showed a significant reduction at Weeks 2 and 4 ($p<0.05$ versus placebo) but not at Week 6. Additionally, response (57.9% versus 36.8%) and remission (42.1% versus 21.1%) rates were numerically higher with quetiapine. No significant differences were observed in AIMS, SAS, BAS, or incidence of AEs. (The most common AEs were fatigue and somnolence.)

Conclusions: Quetiapine may represent a treatment option for patients with GAD. Additional studies are warranted to further characterize the efficacy of quetiapine in these patients.

References:
[1] Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: A double-blind, placebo-controlled study. *J Clin Psychiatry*. 2005;66:1321-1325.
[2] Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: A placebo controlled study. *Biol Psychiatry*. 2005.

Session I - 9

Double-Blind Comparison of Bupropion XL and Escitalopram in Patients with Generalized Anxiety Disorder

Alexander Bystritsky, M.D. [1], Lauren Kerwin, B.A. [1], Tanya Vapnik, Ph.D. [2]

[1]University of California, Los Angeles, [2]Pacific Institute for Medical Research, Los Angeles, CA

Objective: To evaluate the efficacy of Escitalopram (Lexapro) and Bupropion XL (Wellbutrin XL) extended release in the preferential reduction of specific symptoms of generalized anxiety disorder (GAD).

Methods: This study utilized a randomized, double-blind, dose-controlled, parallel-group design. Thirty outpatients with a mean age of 36 years were randomized into one of two treatment groups: Escitalopram (20mg/day) or Bupropion XL (300mg/day). The primary efficacy measures were the mean change from baseline to endpoint in the total score on the Hamilton Anxiety Rating Scale (HARS) and Self-Efficiency Scale (SES).

Results: The baseline scores on HARS/HDRS were $24.88\pm4.58/12.53\pm4.14$ for Escitalopram-treated subjects and $23.08\pm6.60/12.69\pm3.71$ for Bupropion XL-treated subjects. The end point means on the primary dependent variable HARS were 11.0 ± 66.87 for Escitalopram-treated subjects and 4.54 ± 2.75 for Bupropion XL-treated subjects, which demonstrates a significant decrease in anxiety for both treatment groups. ANCOVA demonstrated HARS total score ($F = 9.46$, $p<0.005$) and HDRS total score ($F=0.65$, $p<0.025$) were significantly improved in Bupropion XL-treated subjects compared with Escitalopram-treated patients at endpoint. Moreover, subjects treated with Bupropion XL had significantly lower SES scores than subjects treated with Escitalopram.

Conclusions: Subjects in both groups experienced significant reduction in anxiety symptoms over 12-week treatment period. However, individuals treated with Escitalopram showed a significant reduction in fear symptoms, while individuals treated with Bupropion XL showed significant reductions in self-sufficiency symptoms.

Session I - 10

Venlafaxine XR Treatment in Social Anxiety Disorder: A Pooled Analysis of Response and Remission Rates

Michael Liebowitz, M.D. [1], Jonathan Davidson, M.D. [2], Carlos Blanco, M.D. [1], Raj Tummala, M.D. [3], Qin Jiang, B.S. [3]

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Objective: To compare the efficacy of venlafaxine extended release (XR) versus placebo in the treatment of social anxiety disorder (SAD).

Methods: Data were pooled from five randomized studies of patients with DSM-IV SAD (ITT n=1459) treated with venlafaxine XR (75-225 mg/d) or placebo for 12 weeks; one study lasted 28 weeks. Response (Clinical Global Impressions-Improvement score ≤ 2) and remission (Liebowitz Social Anxiety Scale score ≤ 30) rates were calculated for the overall population, and stratified by gender and physical symptom severity (based on Social Phobia Inventory [SPIN] sweating, blushing, palpitations, and tremor items), and compared between groups using the Fisher exact test (LOCF). The number needed to treat (NNT) was calculated using week 12 remission rates.

Results: Overall response rates were 55% for venlafaxine XR and 33% for placebo (P<0.0001); remission rates were 25% and 12%, respectively (P<0.0001). Women comprised 46% of the population. Response rates were 55% and 32% among venlafaxine XR- and placebo-treated women, respectively (P<0.0001); remission rates were 26% and 12%, respectively (P<0.0001). Among men, response rates were 52% and 34% for venlafaxine XR and placebo, respectively (P<0.0001); remission rates were 25% and 12%, respectively (P<0.0001). The median baseline SPIN physical symptoms score was 9. Among patients with less severe physical symptoms (baseline score ≤ 9; n=661), response rates were 52% and 32% for venlafaxine XR and placebo, respectively (P<0.0001); remission rates were 27% and 14%, respectively (P<0.0001). Response rates among patients with more severe physical symptoms (baseline score >9; n=794) were 56% for venlafaxine XR and 33% for placebo (P<0.0001); remission rates were 24% and 11%, respectively (P<0.0001). In the long-term study, response rates for venlafaxine XR and placebo were 53% and 28%, respectively, at week 12 (P<0.0001), and 58% and 33%, respectively, at week 28 (P<0.0001). Remission rates in the long-term study were 23% for venlafaxine XR and 11% for placebo at week 12 (P=0.005) and 31% and 16%, respectively, at week 28 (P=0.0023). For the overall population, the NNT for remission at week 12 was 8 (95% CI: 6.5, 8.9).

Conclusions: Venlafaxine XR is effective in the treatment of SAD, regardless of gender or severity of physical symptoms.

Session I - 11

Pregabalin's Sustained Efficacy and Long-Term Safety and Tolerability in the Treatment of Generalized Anxiety Disorder and Social Anxiety Disorder: A 1-Year, Open-Label Study

Naomi Simon, M.D. [1], Jerri Brock, M.S. [2]

[1]Massachusetts General Hospital, Boston, [2]Pfizer Global Research and Development, Ann Arbor, MI

Background: Pregabalin has demonstrated efficacy in the treatment of generalized anxiety disorder (GAD) in six short-term trials and one 6-month relapse-prevention trial, and of social anxiety disorder (SAD) in three short-term and one 6-month relapse-prevention study. We report here on pregabalin's maintenance of efficacy, safety, and tolerability in a 1-year, open-label extension study of patients enrolled in clinical trials of GAD and SAD.

Methods: The efficacy-evaluable sample included patients who completed pregabalin short-term double-blind trials for GAD or SAD, and received at least 1 open-label dose of pregabalin (200-600 mg/d, administered BID). Disease severity was assessed by Clinical Global Impression of Severity (CGIS) score (7-point scale) at week 52. Safety and tolerability were also assessed.

Results: Two hundred sixty-five patients (148 women, 117 men) were enrolled; 140 (53%) completed 36 weeks, 68 (26%) completed 52 weeks. Fourteen (5.3%) were 65 years old or older. At open-label entry, 119 patients (44.9%) were rated as not at all to mildly ill (CGIS score <4), and 146 (55.1%) were moderately ill (CGIS score=4) or worse. At 1 year, 187 (75.4%) were rated as not at all to mildly ill, and 61 (24.6%) were rated as moderately ill or worse. Most adverse events were mild-to-moderate in severity. Dizziness, infection, pharyngitis, and somnolence were reported most commonly; 11.3% discontinued treatment because of adverse events.

Conclusions: The anxiolytic efficacy of pregabalin was maintained, and pregabalin was found to be safe and well tolerated for up to 1 year. The severity of anxiety symptoms tended to decrease with extended pregabalin treatment.

Session I - 12

Adjunctive Risperidone in the Treatment of Generalized Anxiety Disorder: A Double-Blind, Placebo-Controlled, Randomized Study

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Background: Refractory residual symptoms remain in a considerable proportion of patients with generalized anxiety disorder (GAD). This study examined the effectiveness of risperidone compared with placebo added to standard care in GAD patients.

Methods: The subjects, patients with a DSM-IV GAD diagnosis who remained symptomatic despite treatment with an anxiolytic agent for ≥8 weeks, received adjunctive risperidone or adjunctive placebo for 6 weeks. The primary effectiveness measure was the patient-rated Most Troubling Symptoms (MTS) scale, comprised of seven GAD symptoms from the DSM-IV, rated on a scale of 0–10 via a telephone interactive voice response system. The primary endpoint was the MTS total score (sum of the four items identified as most troubling by each patient at baseline) at the week-4 endpoint (LOCF).

Results: Data were available for 390 patients; 196 received risperidone and 194 received placebo. The mean (± SD) modal dose of risperidone was 0.9±0.2 mg/day over weeks 1–4. The four MTS items rated by patients as most troubling were excessive anxiety or worry (76%), feeling restless (68%), trouble sleeping (66%), and getting tired easily (55%). Mean MTS total scores were reduced from 29.2±6.6 in the risperidone group and 28.8±6.7 in the placebo group at baseline to 22.3±7.1 and 23.4±7.9, respectively, at week 1 ($P<0.05$ between groups) and to 19.9±9.0 and 21.0±8.8 at the week-4 endpoint ($P<0.001$ vs baseline in both groups). In a post-hoc analysis of MTS primary items rated ≥5 by the patients at baseline, changes in the percentage of the maximum attainable MTS total scores at the week-4 endpoint were –25.8% in the risperidone group and –21.6% in the placebo group ($P<0.05$ between groups). In the total population, on the Patient-Rated Global Improvement Scale, significantly greater improvements were seen at weeks 1 and 3 and at endpoint in patients receiving risperidone than placebo ($P<0.05$). Significantly greater medication satisfaction and life satisfaction (Q-LES-Q scores) were reported by patients receiving risperidone than placebo ($P<0.05$).

Conclusions: Preliminary support of the efficacy of adjunctive risperidone on refractory residual symptoms in GAD patients was observed. The patient-rated MTS appears to be a useful instrument for assessing treatment effects in GAD patients.

Session I - 13

Preliminary Evidence of Short-Term Efficacy of a Novel, Non-Azapirone Selective 5-HT1A Agonist in Generalized Anxiety Disorder

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Background: Although the serotonin 1A receptor likely plays a critical role in anxiety pathophysiology, very few available treatments selectively modulate this receptor. This is the first study to test tolerability and anxiolytic efficacy of PRX 00023, a novel non-azapirone 5-HT1A selective agonist, in adult outpatients with generalized anxiety disorder (GAD).

Methods: Twenty-one patients (9M/12F) aged 20 to 58 years, with a principle DSM-IV diagnosis of GAD and screening Hamilton Anxiety Rating Scale (HAM-A) scores of 20 or greater, received drug in this 4 week open-label study. A one-week, single-blind placebo run-in was followed by a 28-day open-label treatment with PRX 00023 given in the following force-titration protocol: 40 mg (days 1- 4), 80 mg (days 5-14), and 120 mg (days 15-28).

Results: PRX 00023 significantly reduced GAD symptoms from day 1 in all outcome measures, including HAM-A total ($p < 0.01$), CGI-S ($p < 0.01$), and HADS anxiety ($p < 0.02$). At day 28, HAM-A total, psychic, and somatic scores decreased by 10.3, 6.5, and 3.8 points from initial scores of 22.9, 14.4, and 8.5, respectively (all $p < 0.01$). Six of 19 patients with week 4 evaluations (32%) achieved remission criteria (HAM-A less than or=7) and 52% of patients had a 50% or greater reduction in the HAM-A total score. The magnitude of clinical response over the 28-day treatment period decreased 7 days following the last dose of study medication.

There were no serious adverse events (AEs), no discontinuations due to AEs, no withdrawal symptoms, and no reports of ataxia/dizziness or sexual dysfunction. Also, no significant clinical laboratory, vital sign, or ECG effects were observed.

Conclusions: Given its tolerability and preliminary efficacy in a small sample, larger placebo-controlled trials of PRX-00023 in GAD are warranted.

Session I - 14

Generalized Anxiety Disorder (GAD): Treatment with Paroxetine CR

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Background: Clinical trials have demonstrated the efficacy of paroxetine immediate release in treating generalized anxiety disorder (GAD). Studies with paroxetine controlled release (CR) may lend support for the use of this molecule in the management of GAD.

Objective: To evaluate the efficacy and safety of paroxetine CR in GAD treatment.

Methods: This was a double-blind, placebo-controlled trial evaluating the use of paroxetine CR in adult outpatients diagnosed with GAD (DSM-IV criteria). A one week placebo run-in preceded randomization to placebo or paroxetine CR, 12.5mg - 37.5mg daily, for 8 weeks in a flexible dose design. Participating patients had a total baseline score of > 20 on the Hamilton Anxiety Rating Scale (HAM-A). Patients with other axis I disorders, or requiring other psychotropics, or scoring > 18 on the Montgomery Asberg Depression Rating Scale (MADRS), were ineligible. The HAM-A total score change from baseline was the primary efficacy variable (last observation carried forward [LOCF] dataset). Secondary variables included the HAM-A psychic anxiety subscale, and analyses of Clinical Global Impressions, severity of illness (CGI-S), and CGI responders (CGI-I). Frequencies of adverse experiences (AEs) and AE withdrawals constituted the safety assessment.

Results: This study evaluated 327 patients (paroxetine CR=164, placebo=163) who were predominantly Caucasian (78%) and female (64%) with a mean age of 39. At the week 8 LOCF endpoint, paroxetine CR patients had a mean HAM-A change of -11.9, while placebo patients' endpoint change was -10.7. The drug/placebo difference was not statistically significant (p=0.125, 95% C.I. = [-2.78, 0.34]). However, statistically significant differences (p < 0.05) in favor of paroxetine CR were observed for 11 of the 16 prospectively defined secondary endpoints. Among these were the change in the HAM-A psychic anxiety subscale (p=0.026), the CGI-S, (p=0.018) and the CGI-I responder analysis (p= 0.039). Commonly occurring AEs in the paroxetine CR group (> 5% and twice the placebo rate) included abnormal ejaculation, somnolence, and decreased libido. AE withdrawals were low in both groups (placebo=2.5%; paroxetine CR = 5.5%).

Conclusions: Paroxetine CR demonstrated clinically relevant utility in the treatment of GAD, although statistically significant evidence of efficacy was observed on prospectively defined secondary efficacy measures only. Paroxetine CR was well-tolerated; gastrointestinal AEs did not occur commonly and there was a low incidence of AE withdrawals.

Session I - 15

Levetiracetam for Treatment-Resistant Panic Disorder

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Background: Panic disorder (PD) as defined in the DSM-IV (APA, 1994) is a serious and potentially disabling disorder, affecting 3.5-5% of the general population at some point. In addition, uncontrolled PD confers risk for developing additional psychiatric and medical disorders. Despite availability of effective treatments for PD, many patients remain symptomatic even after treatment. This latter finding may be in part due to anxiety-related noncompliance, tolerability problems, under-treatment, or incomplete response to adequate treatment. Levetiracetam is a marketed anticonvulsant which has shown some promise as an anxiolytic.[1]

Objective: The objective of this study is to assess the potential efficacy of levetiracetam in 20 outpatients with PD with or without agoraphobia who had partial but inadequate response to an adequate trial of pharmacotherapy of at least 8 weeks.[2] This preliminary report presents data on the first 10 patients enrolled.

Methods: Patients were healthy males and females ages 18-60 years who met current DSM-IV for PD of at least moderate severity who had at least two panic attacks per month for the past 3 months. Subjects were recruited through the media and by referral from local mental health specialists. All patients provided written consent prior to any study procedures. Patients with clinically non-predominant comorbid anxiety (except PTSD and OCD) or non-bipolar mood disorders were accepted. The main outcome measure was the clinician-rated Sheehan Panic Disorder Scale[3] and several other relevant secondary outcome measures. Levetiracetam was initiated at 250 mg hs for two days, and then 250 mg bid until day 7. The dose was flexibly titrated upward each week to a maximum of 3000 mg according to tolerability and response. Daily dose increments of no more than 1000 mg per week were allowed. The targeted dose range of levetiracetam was a minimum of 1000 mg and a maximum of 3000 mg daily, taken in divided doses.

Results: Seven of 10 subjects (5 women, 2 men) ranging in age from 25-61 years who were enrolled completed the entire 8 week treatment study. Two non-completers were lost to follow-up, and one was a screen failure. Of the 7 completers, 6 were considered responders. The average final levetiracetam dose was 1429 ± 799 (SD) mg daily. Baseline Sheehan Panic Disorder Scale scores were 58.2 ±18.4 (SD) (range 27-80); average final scores were 18.4 ± 13.7. Adverse effects limited dosing in three patients; all achieved 1500 mg for at least one week.

Conclusions: This preliminary report suggests that patients with incomplete pharmacotherapeutic response to standard anti-panic treatment may benefit from adjunctive levetiracetam treatment. If a larger sample continues to reflect this trend, controlled studies may be warranted.

References:
[1]Simon NM et al. An open-label study of levetiracetam for the treatment of social anxiety disorder. J Clin Psychiatry 2004;65:1219-22.
[2]Lydiard, R.B. Resistant Panic Disorder. Current Psychiatry 2003; 2:12-22.
[3]Sheehan DV. The Anxiety Disease. Charles Scribner & Sons New York, 1983.

Session I - 16

Predictors of Treatment Response in Post-Traumatic Stress Disorder (PTSD): Childhood Trauma, Social Rank, Defeat, and Entrapment

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Background: Several treatment options are available for treatment of post-traumatic stress disorder (PTSD), but not all patients respond to those treatments. Presence of depression, anger, and alcohol use have been shown to be higher among those who do not respond to treatments for PTSD.[1] History of childhood trauma has also been linked to poor outcome.[2]

Anxious arousal has been linked with feelings of defeat, entrapment, and other social-rank variables such as external shame and social comparison.[3] Shame, an emotion associated with painful negative evaluation of self, has been linked to PTSD severity.[4] Our objective is to study social rank variables in the treatment response of PTSD.

Methods: Measures of childhood trauma (CTQ), assertiveness (OAS), social comparison (SC), and feelings of entrapment were collected in 15 patients undergoing a randomized controlled treatment trial for PTSD. Subjects were divided into two categories: responders, and non-responders. ANOVA was performed on the baseline characteristics.

Results: Significant correlation was found between scores on Entrapment scale and Defeat scale (0.64) at baseline. Correlation was found between shame (0.59), defeat (0.69), and entrapment (0.65) scores with baseline score on TOP-8. Pearson correlation analyses were done between these variables and the improvement in TOP-8 score. Social rank test (OAS, a measure of external shame) has a significant correlation with change in TOP-8 score (0.91 p=0.0015). Scores on defeat scale showed a similar correlation with change in TOP-8 score (0.74 p = 0.03). Responders had significantly less external shame and defeat feelings.

Conclusions: Social rank variables, external shame, and feelings of defeat may affect the treatment outcomes of PTSD. Evaluation and management of these on a routine basis may help improve the treatment of PTSD.

References:

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[2] Davidson JR. Pharmacotherapy of posttraumatic stress disorder: treatment options, long-term follow-up, and predictors of outcome. J Clin Psychiatry. 2000;61 Suppl 5:52-6; discussion 57-9.

[3] Gilbert P. The evolution of social attractiveness and its role in shame, humiliation, guilt and therapy. Br J Med Psychol. 1997 Jun;70 (Pt 2):113-47.

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Poster # I - 17 was not presented at the meeting.

Session I - 18

Efficacy and Safety of Divalproex Sodium Extended-Release Versus Placebo in the Treatment of Acute Mania

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Objective: Evaluate the efficacy and safety of divalproex extended-release (ER) for the treatment of manic or mixed episodes associated with bipolar disorder.

Methods: A 21-day, randomized, placebo-controlled, multi-center study was conducted in patients 18-65 years old who were hospitalized for acute mania associated with bipolar I disorder. Divalproex ER was initiated at 25 mg/kg/day, and increased 500 mg on Day 3, with a target serum valproate level of 85-125 mcg/mL. Efficacy assessments included the Mania Rating Scale (MRS; primary endpoint) and percentage of responders ($\geq$50% improvement on the MRS), as well as an effectiveness analysis that incorporated efficacy (final MRS $\leq$ 12, final DSS score $\leq$ 13) and tolerability (no premature discontinuation due to an adverse event).

Results: Intent-to-treat efficacy analyses included 364 patients (187 divalproex ER; 177 placebo). The rapid dose titration designed to achieve therapeutic serum concentrations early in treatment yielded a mean serum valproate level of 96.5 mcg/mL on Day 5 with a mean divalproex ER dose of 2874 mg. Divalproex ER produced superior improvements in manic symptoms vs. placebo assessed by the MRS. More divalproex ER patients met responder criteria vs. placebo (48% vs. 34%, respectively; $p < 0.05$), and more divalproex ER patients met effectiveness criteria (38% vs. 26%, respectively; $p < 0.05$). Adverse events associated with divalproex ER included somnolence, dizziness, and gastrointestinal complaints.

Conclusions: Divalproex ER is a safe and effective treatment for manic or mixed episodes associated with bipolar disorder.

Session I - 19

Child Bipolar I Disorder: Diagnostic Characteristics of Outpatients Obtained by Consecutive New Case Ascertainment Versus Volunteers in a Randomized Controlled Trial

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Background: One important question in designing and interpreting intervention studies is whether they will generalize to real world practice. Although there are a number of studies examining this issue in adult mood disorders, there are, to our knowledge, no prior studies investigating the generalizability of treatment study results in child mood disorders. Even in adults, few studies have looked at this topic in the bipolar disorder population. This report examines the representativeness of a randomized controlled trial (RCT) sample versus one obtained by consecutive new case ascertainment, in child bipolar I disorder (BP-I).

Methods: Subjects (N=231) were outpatient participants in either the NIMH-funded Phenomenology and Course of Pediatric Bipolar Disorders (Phenomenology) or the still-recruiting Treatment of Early Age Mania (TEAM) studies. In both studies, subjects needed current DSM-IV BP-I (manic or mixed phase) and a Children's Global Assessment Scale (CGAS) score ≤ 60. All subjects had elation and/or grandiosity. Subjects in the Phenomenology study were obtained by consecutive new case ascertainment from designated pediatric and psychiatric facilities. Subjects in the TEAM study were volunteers from media and community sources. Assessment instruments included the WASH-U-KSADS, given separately to parents about their children and to children about themselves, and the CGAS. Logistic regression was used for comparisons.

Results: Phenomenology and TEAM groups were similar in age (10.6±2.3, 10.4±2.3 years) and other demography. Both had long current episode duration (3.4±2.4, 4.8±2.4 years), marked severity (CGAS: 42.9±7.5, 38.7±6.7), and low lifetime use of any mood stabilizer (33.3%, 23.6%). Many mania symptoms and ultradian cycling, psychosis, and suicidality were significantly more prevalent in the RCT sample.

Conclusions: The differences in prevalence of mania symptoms and characteristics in the Phenomenology and TEAM samples may not be clinically meaningful. For example, a CGAS of 39 compared to a CGAS of 43 or a mean duration of current mania episode of 4.8 years compared to a duration of 3.4 years were all in the severe and chronic range. Both groups had high rates of almost all mania symptoms and of ultradian cycling, psychosis, and suicidality. Even stronger support for the similarity of the two groups is that only 8.0% of the Phenomenology sample would not have fit the RCT criteria. Dissimilar to some adult studies, the TEAM study subjects appear largely representative of clinical child BP-I.

Session I - 20

Quetiapine Monotherapy for Bipolar II Depression: Pooled Results from Two Placebo-Controlled Studies

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Background: This analysis investigated the efficacy and tolerability of quetiapine monotherapy for depressive episodes in patients with bipolar II disorder from two major clinical trials (BOLDER I[1] and II).

Methods: A post-hoc evaluation was conducted in 351 patients with bipolar II depression from two double-blind, randomized, placebo-controlled, 8-week studies of quetiapine (300 or 600 mg/d; once-daily, evening dosing) in patients with bipolar I or II disorder (DSM-IV) exhibiting moderate to severe depression (HAM-D-17 $\geq$20; HAM-D item 1 [depressed mood] $\geq$2; YMRS $\leq$12). The primary endpoint was change from baseline to Week 8 in MADRS total score (analyzed using mixed-effect model, repeated-measures). MADRS and HAM-D scores were assessed weekly.

Results: Improvement in mean MADRS total score from baseline (range 28.6-29.9 for the three groups) was significantly greater with quetiapine 300 and 600 mg/d from the first assessment (Week 1) through to Week 8. The changes from baseline at Week 8 for quetiapine 300 and 600 mg/day and placebo were –17.09, –17.86, and -13.31 (P=0.005 and P=0.001 vs placebo), respectively. MADRS effect sizes for quetiapine 300 and 600 mg/d were 0.45 and 0.54, respectively. Improvements from baseline at Week 8 in mean HAM-D scores were also significantly greater with both quetiapine doses (–14.33 and –15.04) than placebo (–11.33; P=0.001 and P<0.001, respectively). HAM-D effect sizes were 0.51 and 0.63 for quetiapine 300 and 600 mg/d, respectively. Common adverse events included dry mouth (300 mg/d: 48.3%; 600 mg/d: 43.1%; placebo: 13.7%), sedation (40.7%, 36.2%, 7.7%), and somnolence (20.3%, 19.0%, 6.0%). Adverse events were generally mild in intensity in both studies.

Conclusions: This analysis of two major randomized, controlled trials is, to our knowledge, the largest evaluation to date of an atypical, as monotherapy for bipolar II depression. Quetiapine is one of the first agents to demonstrate significant efficacy as monotherapy, compared with placebo, for the treatment of depressive episodes in bipolar II disorder. Quetiapine was generally well tolerated in both studies.

Reference: [1]Calabrese JR, Keck PE, Jr., Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162:1351-1360.

Session I - 21

Safety of Extended-Release Carbamazepine in Combination with Atypical Antipsychotics in Patients with Bipolar Disorder: Results from an 8-Week, Open-Label Study

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Background: An understanding of the effects of polypharmacy in patients with bipolar disorder is of critical importance, given the common use of combination regimens to treat this condition. The current trial focuses on the safety and efficacy of polytherapeutic regimens containing carbamazepine extended-release capsules (CBZ-ERC) (Equetro™; Shire, Wayne, Pa) in the treatment of bipolar disorder. Here, the safety profile associated with the concomitant use of CBZ-ERC and atypical antipsychotics (AAPs) in this trial is discussed.

Methods: The current 8-week, open-label trial involved adult outpatients with acute manic or mixed bipolar symptoms who were receiving antipsychotic monotherapy (olanzapine, risperidone, quetiapine, or aripiprazole) or combination therapy involving a mood stabilizer (lithium, valproate, or lamotrigine) plus an antipsychotic at study entry. At baseline, treatment with CBZ-ERC 200 mg/d was initiated, and doses were optimized within the 200 to 1600 mg/d range over the next 4 weeks. During this dose titration period, concomitant mood stabilizers other than lithium were discontinued via gradual tapering, such that all patients were ultimately receiving CBZ-ERC plus lithium plus an antipsychotic agent or CBZ-ERC plus an antipsychotic only. Upon completion of CBZ-ERC titration, lithium and/or antipsychotic doses were readjusted as necessary, and all drug doses were subsequently maintained at stable levels. Safety and efficacy were evaluated weekly during dose titration and then at study endpoint.

Results: Fifty-three patients were receiving an AAP (most commonly, quetiapine [50.9%] or aripiprazole [28.3%]) at baseline. Adverse events (AEs) arising after the addition of CBZ-ERC to AAP therapy were generally characteristic of the anticonvulsant class and were, in the large majority of cases, mild to moderate. Common AEs (≥10% incidence) included somnolence (26.4%), sedation (22.6%), dizziness (20.8%), headache (17.0%), and nausea (13.2%). Serious AEs were rare, being documented in two patients (abdominal pain [n = 1] and priapism [n = 1]) after the addition of CBZ-ERC to AAP therapy. In addition, nine patients withdrew from the study due to a treatment-emergent AE.

Conclusions: The addition of CBZ-ERC to AAP therapy for patients with bipolar disorder was generally safe and well tolerated. This encouraging finding should be interpreted cautiously, however, given the small, open-label nature of the current trial.

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Session I - 22

Bipolar Inventory Symptoms Scale (BISS)

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Background: Despite much research, bipolar disorder remains poorly understood. One of the reasons for this is a complicated diagnosis. Although the DSM 4 TR has discrete categories, most clinicians and academicians see a spectrum of symptoms. This change in concept has led to ambiguities and lack of clarity in making the diagnosis and determining the severity of the illness. As an alternative to current symptom checklists and severity scales, we developed the Bipolar Inventory Symptoms Scale (BISS) that has a pirori defined symptom subgroups encompassing both the historical categories and spectrum symptomatology. This study is a preliminary analysis to determine if the BISS factors (questions) are on the right track to measure both the traditional and spectrum mood states.

Methods: All subjects had a diagnosis of bipolar 1 or 2 by M.I.N.I. They were classified as manic N=4, mixed N=6, depressed N=5, and recovered N=5. The BISS is 41 items with scores ranging from 0-symptom not present; 1-slight to 2-mild; 3-moderate; to 4-symptom is severe with significant impact on life. The clinicians instructed the subjects to limit their answers to the last 7 days. The Interview was performed by six trained raters using a standardized script and videotaped. Twenty interviews were viewed and independently rated by nine clinicians.

Statistics: The mean item score over the nine raters was used. We used a Promax rotation of the mean item score as an exploratory approach to identify underlying factors. Student T tests determined rank order. Pearson correlations were used to identify between factor correlations and Chronbach's alpha and ANOVA were used for subscale reliability.

Results: Nine latent factors were identified. Their reliability (Chronbach alpha) and validity (ANOVA) were supported. DSM 4 TR recovered phase was significantly associated with seven factors, depressed phase with three factors, mixed phase with two factors, and manic phase one factor. Depressive cognition/anergia, manic energy, and irritability factors are the most closely associated with the DSM 4 TR depressed, manic, and mixed criteria. In addition, psychotic, anxiety, lability, emotional distress, manic cognitions, and psychological distress factors explained other aspects of bipolar disorder symptomatology.

Conclusions: In an attempt to tease apart the underlying bipolar disorder symptomatology and better rate their severity we developed the BISS. We have previously shown the reliability of the scale and now in a preliminary factor analysis have identified as many as nine latent factors. Of these factors, three coincide with the DSM groups. Interestingly, the six additional factors explain as much or more of the observed variance as the DSM groups. These factors or subscales, along with the a priori ones, will provide information for later confirmatory factor analysis with larger sample sizes.

Session I - 23

Medication Adherence Skills Training for Middle-Aged and Elderly Adults with Bipolar Disorder: Development and Pilot Study

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Background: Older adults with bipolar disorder experience high rates of disability and have special risks for poor adherence to medications (e.g, cognitive impairment, polypharmacy), yet no augmentative behavioral treatments to enhance adherence have been developed for this group of patients. We present the rationale, development, and pilot study of a medication adherence skills training (MAST-BD) intervention for older adults with bipolar disorder. The intervention is a 12-week manualized group intervention that combines educational and cognitive-behavioral components with skills training in medication management skills adapted for older adults.

Methods: Among 21 older outpatients with bipolar disorder (mean age=60 years; sd=6), the feasibility and acceptability of MAST-BD were assessed in a quasi-experimental clinical trial. We also obtained preliminary effect sizes associated with pre-post change on measures of self-reported adherence to psychiatric medications, performance-based medication management ability, attitudes toward medication, depressive and manic symptoms, and health-related quality of life.

Results: At baseline, 55% of participants reported recent non-adherence to psychiatric medications and were, on average, suffering from moderately severe depressive symptoms and minimal symptoms of mania. A total of 76% of participants completed the intervention, and 86% of sessions were attended by completers. Participants reported high satisfaction with the intervention and manual. Pre-post improvement by small to medium effect sizes (Cohen's d=0.30-0.57) was seen in medication adherence, medication management ability, depressive symptoms, and selected indices of health-related quality of life.

Conclusions: Notwithstanding limitations of this small preliminary study, results are encouraging that the MAST-BD intervention was feasible, acceptable to patients, and associated with improvement in key outcomes. Suggestions for further development of medication adherence interventions for this neglected group of patients are discussed.

Poster # I - 24 was not presented at the meeting.

Session I - 25

Increased Mood Episode Cycling with Antidepressants in Bipolar Disorder: A Randomized Clinical Trial

Vanessa A. Stan, B.A. [1], Benjamin Zablotsky, B.A. [1], David J. Borrelli, M.D. [2], Michael J. Ostacher, M.D. [2], Rif S. El-Mallakh, M.D. [3], Claudia F. Baldassano, M.D. [4], Robert T. Dunn, Ph.D., M.D. [1], Megan M. Filkowski, B.A. [5], Gary S. Sachs, M.D. [2], Fredrick K. Goodwin, M.D. [6], Ross J. Baldessarini, M.D. [7], S. Nassir Ghaemi, M.D. [5]

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Background: Previous studies conflict about long-term antidepressant treatment of bipolar depression. Some double-blind placebo controlled data suggest that tricyclic antidepressants may worsen the course of rapid-cycling bipolar disorder,[1] while other observational data in non-rapid cycling bipolar patients suggest that antidepressant discontinuation leads to more depressive relapse.[2] This is the first randomized study of antidepressant discontinuation in long-term treatment of bipolar disorder with modern antidepressants.

Methods: In interim analysis of 5-year study (n=66), subjects recovered from a depressive episode on mood stabilizer plus antidepressant were openly randomized to continue (LT; n=30) or discontinue (ST; n=36) antidepressants. Subject mood was noted at each visit with measures of affective morbidity. Data are presented as adjusted in regression models for rapid cycling, gender, age, substance abuse, psychosis, and antidepressant attitude.

Results: ST group had fewer depressed episodes (ß=-0.55, 95% CI[-1.48, 0.39]). ST group had a slight, though statistically insignificant, benefit over LT group for number of manic episodes observed (ß=-0.082; 95% CI[-0.42, 0.25]).

Conclusions: These data are consistent with superiority of antidepressant discontinuation, compared with antidepressant continuation, in terms of mood episodes observed. Antidepressant continuation was associated with increased mood episode cycling rates, even in a mostly non-rapid cycling population.

References:
[1]Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987; 144(11):1403-1411
[2]Altshuler LL, Suppes T, Black D, Nolan WA, Keck PE Jr, Frye MA, McElroy S, Kupka R, Grunze H, Walden J, Leverich G, Denikoff K, Luckenbaugh D, Post R: Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry 2003; Jul;160(7):1252-62

Session I - 26

Efficacy of Quetiapine Monotherapy in Bipolar Depression: A Confirmatory Double-Blind, Placebo-Controlled Study (The BOLDER II Study)

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Background: The BOLDER II study is the second major clinical trial to evaluate the efficacy and tolerability of quetiapine monotherapy for depressive episodes in bipolar disorder.

Methods: Similar to the BOLDER I study,[1] patients with bipolar I or II disorder (DSM-IV) exhibiting moderate to severe depression (HAM-D-17 $\geq$20; HAM-D item 1 [depressed mood] $\geq$2; YMRS $\leq$12) were randomized to 8 weeks of double-blind treatment with quetiapine (300 or 600 mg/d; once-daily, evening dosing) or placebo. Patients were assessed weekly using MADRS and HAM-D. The primary endpoint was change in MADRS total score from baseline to Week 8 (ANCOVA/LOCF analysis).

Results: Of 509 patients randomized, 59% completed the study. Improvements from baseline in mean MADRS scores were significantly greater from the first evaluation at Week 1 with quetiapine 300 (–9.42) and 600 mg/d (–9.14) than with placebo (both $P<0.001$ vs placebo –6.10) through to Week 8 (quetiapine 300 and 600 mg/d: –16.94 and –16.00 respectively; both $P<0.001$ vs placebo: –10.2). MADRS effect sizes at Week 8 were 0.54 and 0.61 for quetiapine 300 and 600 mg/d, respectively. Improvements in mean HAM-D scores were also significantly greater with both quetiapine doses than with placebo ($P<0.001$) throughout the study (Week 8 effect sizes 0.61 and 0.55 for 300 and 600 mg/d, respectively). There were significant improvements in primary and secondary outcomes with both 300 and 600 mg/d quetiapine, without major differences between the two doses. Common AEs included dry mouth, sedation, somnolence, and dizziness. Generally, AEs were mild in intensity; discontinuation rates due to AEs were 8.1% (300 mg/d), 11.2% (600 mg/d), and 1.2% (placebo).

Conclusions: These results replicate those of the BOLDER I study[1] and confirm that quetiapine monotherapy is effective and well tolerated for bipolar I and bipolar II depressions.

References: [1]Calabrese JR, Keck PE, Jr., Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162:1351-1360.

Session I - 27

Prevalence of Bipolar Disorder Risk Among Anti-Depressant Non-Responders

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Background: The objective of this study was to assess the rate of bipolar disorder (BPD) risk among patients currently in treatment for Major Mood Disorder (MDD).

Methods: Psychiatrists from community and private practice clinic settings randomly selected patients with unipolar depression who had one or more prior antidepressant (AD) medication failures. Patients with a physician diagnosis of BPD, OCD, or schizophrenia were excluded. Medical record abstraction obtained patient history as well as current and prior AD medication use. A self-administered patient survey collected demographics, bipolar symptoms via the Mood Disorder Questionnaire (MDQ), and co-morbid health problems for self.

Results: Data were collected from 602 patients. A total of 18.6% of patients screened positive on the MDQ and this rate was not impacted by the number of prior AD failures or patient demographics. There were 74 patients (12.3%) who reported a prior history of BPD that was not diagnosed by the psychiatrist. The positive MDQ rate in this subgroup was 41.9%.

Conclusions: These data suggest that clinicians should carefully screen for BPD among their unipolar patients, regardless of AD treatment history or demographic sub-group. Further consideration should be given to identifying and evaluating those with prior BPD history.

Session I - 28

Hepatic Enzyme Stability in Actively Drinking Bipolar Patients Randomized to Divalproex Sodium or Olanzapine

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Objective: To evaluate hepatic enzymes in actively drinking bipolar patients randomized to either Divalproex Sodium (DVPX) or Olanzapine (OLZ).

Background: The cause of hepatic enzyme elevation in bipolar disorder complicated by comorbid alcoholism may be related to alcohol or hepatically metabolized drugs. This study evaluated whether treatment of alcohol abuse/dependence in bipolar disorder with hepatically metabolized drugs compromises hepatic function.

Methods: Fifty subjects (31M /19W, 33 BPI/17BPII, mean age 35.1 +/- 10.9 yrs) participated in a 52-week, single rater blind randomization to either DVPX or OLZ (26DVPX / 24OLZ). Hepatic function tests were collected at baseline and at each study visit. Subjects with hepatic function tests greater than 3 times the normal limit were excluded.

Results: Baseline and exit hepatic enzymes were measured. In the month prior to randomization, the Time Line Follow Back (TLFB) reported 19.12 +/- 9.41 drinking days, 9.69 +/- 5.76 drinks per drinking day, and 176.30 +/- 145.01 total standard drinks for the entire cohort. As presented in Table 1, at study exit, the subjects randomized to DVPX (N=26, mean days in study = 101.7 +/- 109 days) and OLZ (N=24, mean days in study = 54.4 +/- 69 days) showed no significant hepatic compromise within the study period.

Figure 1. Mean hepatic enzyme levels prerandomization and as a function of medication randomization at study exit.

Hepatic Enzyme (Reference Range)	Prerandomization (N=50)	DVPX Final Visit (N=26)	OLZ Final Visit (N=24)
Bilirubin , Total (0.2-1.5 mg/dl)	0.78 +/- 0.27	0.8 +/- 0.27	0.74 +/- 0.30
ALK (35-110 U/L)	56.2 +/- 12.48	50.23 +/- 10.97	57.25 +/- 13.73
ALT (5-50 U/L)	26.2 +/- 14.58	25 +/- 15.89	32.79 +/- 29.45
AST (15-50 U/L)	26.32 +/- 10.50	27.73 +/-15.07	29.37 +/- 16.22
Amylase (29-165 U/L)	67.6 +/- 25.36	74.41 +/- 30.55	75.91 +/- 30.73
GGT (5-50 U/L)	31.4 +/- 24.06	24.82 +/- 10.95	28.52 +/- 29.97

Conclusions: This study is limited by its small sample size and acute study duration. While the data suggest no significant hepatic compromise in this comorbid population, careful monitoring of hepatic enzymes is strongly recommended over the course of treatment.

Session I - 29

Antidepressant-Related Relapse in Bipolar Disorder

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Objective: Some studies suggest that antidepressant continuation improves outcomes following recovery from bipolar depression. We report interim data from the first randomized controlled trial to assess if antidepressant discontinuation with new generation agents leads to an increased risk of relapse in bipolar disorder.

Methods: Subjects recovered from a major depressive episode for 2 months (on mood stabilizer plus antidepressant) were openly randomized to either continue (LT; n=30) or discontinue (ST; n=33) antidepressants, with at least 1 year follow-up. A questionnaire (rated -2 to +2 each) measuring patient opinion on antidepressant use was administered prior to randomization.

Results: A partial analysis was conducted (n=66). In an unadjusted survival analysis of time to first mood episode, the ST group seemed more likely to relapse (HR=1.77, 95% CI [1.45, 2.15]). After adjusting imbalanced covariates, the ST group was more likely to relapse (HR=0.13, 95% CI [0.08, 0.22]). Apparent superiority of antidepressant continuation in univariate analysis may reflect confounding bias. Patient expectation (attitude) was a major confound to informal clinical observations.

Conclusions: Observational evidence of antidepressant benefit is likely due to confounding bias. Randomization and adjustment for confounders demonstrate increased depressive relapse with antidepressant continuation. Data will be updated prior to presentation.

References:

Altshuler L, Suppes T, Black D, Nolen WA, Keck PE, Jr., Frye MA, McElroy S, Kupka R, Grunze H, Walden J, Leverich G, Denicoff K, Luckenbaugh D, Post R: Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry; 2003; 160(7):1252-62

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: A report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry; 1984; 41:1096-1104.

Session I - 30

Efficacy of Ziprasidone in Dysphoric Mania: Pooled Analysis of Two Double-Blind Studies

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Background: Dysphoric mania is a common and often difficult to treat subset of bipolar mania associated with significant depressive symptoms. This post-hoc analysis evaluated the efficacy of ziprasidone in the treatment of depressive and other symptoms in patients with dysphoric mania.

Methods: Data were pooled from two similarly designed, randomized, double-blind, placebo-controlled 3-week bipolar mania trials. Patients were considered to have dysphoric mania if they had a score of ≥ 2 on at least two of the following items of the SADS-C: 1–6, 16, and 20 (extracted HAM-D). Changes in depressive symptoms were measured by the extracted HAM-D on days 2, 4, 7, 14, and 21 and evaluated by MMRM analysis. Additional assessments included changes in scores on the MRS, CGI-S, PANSS, and GAF scale.

Results: HAM-D scores were significantly lower at all visits starting on day 4 in the patients who received ziprasidone than in the patients who received placebo ($P<0.05$). Mean change ($\pm$SD) from baseline to endpoint (21 days) was -4.2 ($\pm$0.7) in the ziprasidone group and –2.1 ($\pm$1.0) in the placebo group ($P=0.027$). Ziprasidone-treated patients also demonstrated significant improvements on the MRS, CGI, PANSS, and GAF scores compared to placebo.

Conclusions: In acute placebo-controlled trials, treatment with ziprasidone provided significant improvement in patients with dysphoric mania.

References:

McElroy SL, Keck PE Jr, Pope HG Jr, et al. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry.* 1992;149:1633-1644

Session I - 31

Comparative Efficacy of Twice-Daily and Once-Daily Extended-Release Carbamazepine in Bipolar Disorder: Results from a Double-Blind, Parallel-Group Trial

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Background: Carbamazepine extended-release capsules (CBZ-ERC) (Equetro™; Shire, Wayne, PA) have been shown to possess significant efficacy in reducing symptoms of acute bipolar mania when administered using a twice-daily (bid) schedule. However, retrospective data suggest that once-daily CBZ-ERC dosing may have similar efficacy in the treatment of acute bipolar mania. To evaluate this hypothesis, a prospective trial comparing the efficacy of a standard bid dosing regimen with that of a once-nightly (qhs) CBZ-ERC regimen in patients with bipolar disorder was conducted.

Methods: The current 12-week, double-blind study involved adult outpatients experiencing either a manic or mixed bipolar episode at study entry. Trial participants were randomized to receive CBZ-ERC on either a bid or a qhs schedule. In both treatment groups, patients received a total CBZ-ERC dose of 200 to 1600 mg/d, with dose titration performed over the first 4 weeks post-baseline. Efficacy and safety were assessed at weeks 1, 2, 3, 4, 6, 8, and 12.

Results: In the intention-to-treat population (bid, n = 52; qhs, n = 53), least-squares mean changes in Young Mania Rating Scale scores relative to baseline showed no statistical difference between treatment arms at week 1 (bid, -5.3; qhs, -5.0; P=.841), and similar findings were made at all subsequent time points out to week 12 (bid, -11.4; qhs, -10.1; P=.325 [last observation carried forward {LOCF}]). The bid and qhs schedules also had comparable effects on overall disease severity (measured using the Clinical Global Impressions Scale–Bipolar Version) at all time points from week 1 onward, with 50.0% of bid-treated patients and 41.5% of qhs-treated patients classified as "much improved" or "very much improved" at study endpoint (P=.534). With regard to depressive symptoms, both treatment regimens yielded similar mean improvements in Hamilton Depression Rating Scale (P=.100 [LOCF]) and Montgomery-Åsberg Depression Rating Scale scores (P=.302 [LOCF]) at all post-baseline time points.

Conclusions: Once-nightly and bid dosing of CBZ-ERC appear to be similarly effective in reducing the severity of acute bipolar mania, as well as in reducing depressive symptoms and overall disease activity in patients with acute manic or mixed bipolar disorder. These findings suggest that qhs dosing of CBZ-ERC may represent an effective alternative to bid dosing.

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Session I - 32

Effect of Antidepressants on Long-Term Mood Morbidity in Bipolar Disorder: A Randomized Study

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Objective: Previous studies suggest that TCAs may worsen the course of bipolar disorder, or may be ineffective in bipolar depressive prophylaxis. Many believe modern antidepressants are more effective and safe. This is the first randomized study of long-term outcome in bipolar disorder with modern antidepressants.

Methods: In interim analysis of this 5-year study (n=66), subjects first recovered from a depressive episode on mood stabilizer plus antidepressant were openly randomized to continue (LT; n=30) or discontinue (ST; n=36) antidepressants (up to 1-year follow-up presented). Primary outcome was total affective morbidity at one year (sum of subscale ratings for mania + depression at follow-up visits) on the Clinical Monitoring Form (CMF; scores: 0 euthymia; 1–6 subsyndromal; >6 syndromal depression or mania; 1 point = 1 DSM-IV mood episode criteria). A questionnaire (rated -2 to +2 each) measuring patient opinion on antidepressant use was administered prior to randomization.

Results: LT treatment had no effect on mood episode criteria after adjusting for other clinical variables (CMF difference=1.32 points, 95% CI:–0.48, 3.14). Rapid cycling, negative attitudes, and prior psychosis predicted more overall morbidity for staying on antidepressants. In adjusted models, the ST group had less long-term morbidity or need to change treatment. Neither depressive nor manic morbidity increased with continued treatment, after adjusting for other variables (CMF difference=0.18 points, 95% CI:–0.48, 0.83, & CMF difference=0.92 points, 95% CI: –0.42, 2.26, respectively). There was evidence of more adjusted depressive morbidity in the RC subgroup with LT vs. ST groups (CMF=2.02 points, 95% CI: -0.06, 4.10).

Conclusions: Findings are consistent with non-inferiority of AD discontinuation. Modern ADs did not reduce long-term BP depressive morbidity. Long-term antidepressant use appeared associated with more depressive morbidity in the rapid cycling subgroup. Data will be updated prior to presentation.

References:

Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987; 144(11):1403-1411.

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: A report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984; 41:1096-1104.

Session I - 33

Brain Metabolites Are Altered in Frequently Relapsing Bipolar Patients Treated with Long-Acting Risperidone

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Background: Studies of bipolar patients using magnetic resonance spectroscopy (MRS) have shown that lactate and glx (glutamate + glutamine + gamma-aminobutyric acid) are increased in gray matter and that treatment alters glx and myo-inositol (mI) levels. Reductions in levels of N-acetylaspartate (NAA), a marker of neuronal integrity, have also been demonstrated in these patients and may be associated with treatment response in mania. Atypical antipsychotic medications have been shown to be effective in the treatment of bipolar disorder; however, their neurochemical effects in this disorder are not well characterized.

Methods: Spectra were obtained for 13 subjects with frequently relapsing bipolar disorder enrolled in a clinical trial of long-acting risperidone augmentation. All subjects continued with their treatment as usual (TAU) and were scanned before and after 6 weeks of risperidone augmentation. Thirteen non-psychiatric control subjects also completed the MRS protocol. All imaging data were acquired on a Varian 4 Tesla scanner using 2D magnetic resonance spectroscopic imaging.

Results: Bipolar subjects had lower baseline levels of whole brain glutamate (glu) and myo-inositol compared to controls ($p<0.02$). Following treatment, changes in whole brain NAA concentration were significantly different between subjects with and without clinical improvement on the Young Mania Rating Scale (YMRS) ($p<0.05$). Lateral frontal cortical NAA was also significantly lower for subjects who demonstrated increased YMRS scores following treatment ($p<0.02$). Glu levels were also significantly reduced following treatment ($p<0.002$) within this region. Notably, these reductions in Glu showed a trend correlation ($p=.08$) with reduced scores on the Montgomery Asberg Depression Rating Scale (MADRS) following treatment.

Conclusions: Changes in NAA and Glu concentration in bipolar patients treated with Risperdal Consta correlated with clinical measures. Previous investigations have suggested that reductions in NAA, which is synthesized in mitochondria, may indicate a bioenergetic dysfunction. Interestingly, baseline levels of Glu concentration were reduced in bipolar patients relative to controls, and were further reduced with treatment, consistent with a reduction in excitatory neurotransmission. These findings indicate that long-acting injectable risperidone impacts neurochemical measures that are associated with symptom improvement.

Session I - 34

Increased Inpatient Psychotropic Polytherapy with Stable Antipsychotic Use in 2004 vs. 1998

Franca Centorrino, M.D. [1], Stephanie L. Cincotta, B.A. [2], Alessandra Talamo, M.D. [2], Kate V. Fogarty, B.A. [2], Mark G. Saadeh, M.D. [2], Francesca Guzzetta, M.D. [2], Paola Salvatore, M.D. [3], Ross J. Baldessarini, M.D. [1]

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Background: Use of combinations of antipsychotic agents with other psychotropics is increasingly prevalent in psychiatric inpatient settings. We reviewed current polytherapy practices at a major psychiatric teaching hospital, comparing current findings with prior samples, to evaluate changes in psychotropic prescription practices for inpatients given antipsychotics.

Methods: We reviewed medical records of McLean Hospital inpatients treated with an antipsychotic for ≥ 3 consecutive days during a 3-month sample (March–May, 2004) to analyze patterns of combining antipsychotics with other antipsychotics, or with mood-stabilizers, antidepressants, or sedatives, and compared results with those for 1998.

Results: The 2004 study sample included 305 patients (60% women; aged 44 ± 17 years) with diagnoses ranking: major affective (53%) > psychotic (32%) > other (15%). Between 1998 and 2004, the per-person count of psychotropic drugs prescribed at discharge to antipsychotic-treated inpatients nearly doubled (from 1.6 to 3.0 agents/patient), as the proportion of patients discharged with ≥ 2 psychotropics increased 3.5-fold (from 25% to 86%). In both years, antipsychotic prescriptions at discharge were similar in number/person and total daily dose, but in 2004 there were 2.1- to 6.1-fold more discharge prescriptions for mood-stabilizers, antidepressants, and sedatives. Patients with major affective diagnoses received more antidepressant prescriptions, and more total agents/person, than those with primary psychotic or other diagnoses. Higher discharge psychotropic prescription counts/patient were independently associated with female sex, but not with length of hospitalization. At discharge, higher chlorpromazine-equivalent primary antipsychotic dose associated independently with higher admission Clinical Global Impression (CGI) score. Patients treated with first-generation antipsychotics received 24% more psychotropics/person (3.6 vs. 2.9) and 96% more mood-stabilizers/person (0.86 vs. 0.44) at discharge than those given modern antipsychotics.

Conclusions: Antipsychotic-treated inpatients received more prescriptions at discharge for mood-stabilizers, antidepressants, and sedatives, but not more antipsychotics or higher total daily antipsychotic doses, in 2004 than in 1998.

Session I - 35

Predictors of Bipolar Disorder Risk Among Patients Currently Treated for Major Depression

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Background: A substantial number of patients with bipolar disorder (BPD) are incorrectly diagnosed as having unipolar depression, and often do not respond adequately to treatment with antidepressant (AD) medication. This study sought to identify predictors of bipolar disorder risk among patients treated for major depressive disorder (MDD).

Methods: Psychiatrists from community and private practice clinic settings randomly selected patients who demonstrated one or more antidepressant medication failures during the current episode of MDD. Patients with BPD, OCD, or schizophrenia were excluded. Patient history and AD use were obtained via record abstraction. Patients self-reported their demographics, family history, co-morbid health status, alcohol/drug use, legal problems, and current depression symptoms via Centers for Epidemiologic Studies - Depression (CES-D) scale. BPD screening was self-reported via the Mood Disorder Questionnaire (MDQ).

Results: Among 602 participants enrolled in the study, the base MDQ positive rate was found to be 18.6%. Stepwise logistic regression identified five variables associated with bipolar disorder risk (MDQ+): The CES-D item "people were unfriendly" (Odds Ratio:(OR)=2.59, p<.001), co-morbid anxiety (OR=2.98, p<.002), depression diagnosis within five years (OR=2.47, p<.001), family history of BPD (OR=2.01, p<.010), and legal problems (OR=1.74, p<.026). For patients with no risk factors (n=41), 2.4% were MDQ+. For patients endorsing "people were unfriendly" (n=103), 31.1% were MDQ+; adding co-morbid anxiety (n=82) increased MDQ+ rate to 35.4%; adding recent depression onset (n=17) increased MDQ+ rate to 41.2%; adding family history (n=4) increased MDQ+ rate to 75%; 100% of those endorsing all five factors (n=3) were MDQ+. For patients endorsing any three or more risk factors (n=109), 41.3% were MDQ+.

Conclusions: Over one-third of depressed patients who suffered from co-morbid anxiety and experienced projection or rejection sensitivity via endorsement of the CES-D item "people were unfriendly," were determined to be at risk for BPD as indicated by a positive score on the MDQ. These two clinical features, along with recent depression onset, BPD family history, and legal problems, may prove useful indicators of BPD risk among patients with difficult to treat depression.

Session I - 36

Prediction of Response to Lamotrigine and Placebo for Bipolar Depression: A Clinically Useful Probability Analysis

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Objectives: Lamotrigine is frequently prescribed for patients with bipolar depression. This is the first study that examines the probability of response at the end of a trial of lamotrigine by week for the treatment of bipolar depression.

Methods: Data were pooled from three randomized placebo-controlled studies that included 579 patients with bipolar I or II disorder and who had a major depressive episode. Full response was defined as $\geq 50\%$ decrease in HAMD-17 without emergence of mania or hypomania. Conditional probability of response at 7 weeks was calculated for minimal (<30% improvement), partial (30-49% improvement), and full response at weeks 1 through 6.

Results: The majority of patients with a full response at each week were also full responders at the end of the trial (75-90%) in both the placebo and lamotrigine treatment groups, with a generally higher proportion of lamotrigine treated patients responding. A greater number of lamotrigine treated patients with partial response at each week (37%-76%), compared to placebo treated patients (18%-48%) were also full responders at the end of the trial. Lamotrigine-treated patients with minimal response at weeks 1, 2, 3, 4, 5, and 6 were less likely to be full responders by week 7, with 53%, 43%, 38%, 24%, 27%, and 11%, respectively.

Conclusions: As minimal response persisted, patients had a declining probability of final response. Those with partial and full response at each time point were more likely to continue as responders by the end of the trial.

Source of Funding: GlaxoSmithKline

Session I - 37

Preliminary Reliability and Validity of a Measure to Evaluate Core Symptoms of Autism: The Ohio Autism Clinical Impressions Scale (OACIS)

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There are few measures available for evaluating the core symptoms of autism spectrum disorders, and even fewer options for evaluating changes in core symptoms as a function of treatment or intervention. The best available measures have not yet been demonstrated to be reliable and valid measures sensitive to change in the core symptoms, such as increases in reciprocal social interactions, increases in communication skills, and decreases in restricted, repetitive behaviors. Efforts currently under way by other researchers to establish a measure of the core symptoms, of autism that would possibly be sensitive to change are encouraging steps, but still the best of these measures would likely be burdensome in large clinical trials. We developed the Ohio Autism Clinical Impressions Scale (OACIS) to be an efficient, brief measure of the core symptoms of autism that would be sensitive to intervention effects, both pharmacological and psychosocial. The OACIS is a 10-item, clinician or teacher completed measure based upon interview and/or observation. Each of nine items represents a rating of the severity of a specific symptom associated with autism spectrum disorders, while one item is a global rating of autism severity. Each item is rated on a 7-point scale, with higher numbers representing greater symptom severity. The measure was completed with both a clinic-based sample (n=31) by physicians or psychologists and a school-based sample (n=37) by teachers. Feasibility assessment suggested that the measure was easy to complete, required no additional training of the evaluators, and could be completed in less than 10 minutes after routine clinical interview or by a familiar teacher. Inter-rater reliability was adequate; specifically, $r=.68$ with the physician/psychologist completed measure, and $r=.52$ with the teacher completed measure. Internal-consistency reliability was strong ($\alpha= .94$). One week test-retest reliability was excellent ($r=.96$). Exploratory factor analysis suggested the possibility of two sub-domains, a "behavioral/developmental" sub-scale and an "emotional" subscale. Validity was evaluated against the Gilliam Autism Rating Scale (GARS), the Aberrant Behavior Checklist (ABC), and the Pervasive Developmental Disorders Behavior Inventory (PDDBI), with correlations ranging from $r=.57$ to $r=.75$. Data collection related to the OACIS' ability to identify changes in core symptoms related to treatment or intervention is on-going. We are also collecting pilot data on a parallel "Improvement" scale to be used in conjunction with the severity ratings.

Session I - 38

Ziprasidone in Early Onset Schizophrenia and Schizoaffective Disorder

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Background: Despite greater sensitivity among youth to antipsychotic-associated weight gain, there have been no systematic studies of ziprasidone in early onset of schizophrenia spectrum disorders. This multisite, open study seeks to provide pilot data regarding antipsychotic and adverse effects of ziprasidone over one year in youth age 8-18 with early onset schizophrenia spectrum disorders.

Methods: All treatment was open–label. Dose was determined by response and side effects. Inclusion criteria required significant psychotic symptoms and DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder. The primary outcome measure was responder status. Secondary outcomes included change in Positive and Negative Symptom Scale (PANSS) total score and adverse events.

Results: Forty patients (mean age 13.90 years) participated. Twenty-six completed at least 8 weeks of treatment and 11 completed 52 weeks. The mean final dose was 117.8mg (STD of 49.2 mg).

All subjects were severely ill at baseline with a PANSS total mean score of 95.90 (24.65). Among responders, PANSS mean dropped by 36%, whereas overall PANSS dropped by only 6%.

Twenty-one subjects experienced notable activation, including 9 who developed frank mania or hypomania. Activation generally led to withdrawal. Sedation, anxiety, and insomnia were the predominant side effects during the acute phase of treatment. There were few significant extrapyramidal side effects, with Simpson Angus Extrapyramidal Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale (AIMS) showing downward trends.

A clinically insignificant QTc prolongation of approximately 5 milliseconds was observed. Fasting and random glucose and lipids were stable. Weight gain tended to be more rapid during acute treatment but slowed significantly during prolonged treatment. In robust responders, weight gain in the first 8 weeks was 11.8 kg and only 2 kg during remainder of treatment.

Conclusions: Ziprasidone was an effective antipsychotic in 42.5% of youth treated in this study, and it had a good metabolic profile, but was associated with marked acute weight gain. Activation frequently led to discontinuation.

Session I - 39

Are Physicians' Estimates an Adequate Measure of Adherence in Youth with Depression?

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Background: Major depressive disorder (MDD) is a serious psychiatric disorder in children and adolescents where antidepressant adherence remains an important issue. Physicians' estimates are one of the most common methods of monitoring adherence due to minimal cost and convenience.

Methods: Sixteen subjects (8 male, 8 female, mean age 10.7) who met DSM-IV criteria for MDD participated in a randomized controlled trial involving SSRIs. This subset of patients' medication adherence was monitored for up to 12 weeks using electronic monitoring (MEMS caps), physician estimates of adherence, and pill counts.

Results: Data indicate that out of 16 patients, physicians hypothesized that only one patient was noncompliant. This patient's pill counts reflected possible nonadherence (67.8%). Physicians failed to identify three other patients whose electronic monitoring data suggested noncompliance (<80%). Nonetheless, physicians' subjective estimation of clinical response was more congruent with objective measures of response, independent of their assessment of medication adherence.

Conclusions: Consistent with the adult literature on medication adherence, physicians overestimate adherence rates in children and adolescents with depression, as electronic monitoring and pill counts do not support their estimates.

Session I - 40

Open-Label Memantine in Children and Adolescents with Pervasive Developmental Disorders

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Objective: There are no drugs that effectively treat the core social impairment in autism. The purpose of this study was to examine the effectiveness and tolerability of memantine for social impairment in children and adolescents with pervasive developmental disorders (PDDs).

Methods: Medical records of 18 consecutively treated patients with PDDs treated with memantine were reviewed. The data included prospectively obtained assessments of severity (S) and improvement (I) using the Clinical Global Impressions Scale (CGI). Pre-trial and follow-up parent ratings were available on six patients using the Aberrant Behavior checklist (ABC). Individual response was defined as a rating of "much improved" or "very much improved" on the CGI-I subscale.

Results: Eighteen patients (15 male, 3 female) (mean +/- SD age = 11.4 +/- 3.3 years; range 6-19 years) received memantine (mean +/- SD dosage = 10.1 +/- 6.3 mg.day; range 2.5-20 mg/day) over a mean duration of 19.3 +/- 19.6 weeks (range, 1.5-56 weeks). Twelve (66%) of 18 patients were judged "responders" to memantine; the mean CGI-I score for the entire group was 2.38 +/- 1.3 (much improved). A statistically significant improvement (p=0.03, n=18) was found between a mean baseline CGI-S score of 4.2 +/- 0.82 and a post-trial score of 3.77 +/- 0.8. Among secondary measures, ABC Hyperactivity subscales scores showed significant improvement (p=0.03) after treatment with memantine. Improvement was also reported in symptoms of social withdrawal. Adverse effects occurred in seven of the 18 (39%) patients and led to drug discontinuation in 4 of the 18 (22%) patients.

Conclusions: In this open-label retrospective study, memantine was effective in improving inattention and social withdrawal in a number of patients with PDD. Controlled studies are warranted to further assess the efficacy of memantine in PDD.

Session I - 41

Intermittent Explosive Disorder: A Diagnosis for Drug Trials in Aggression

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Objective: Aggression is a target symptom for drug treatment studies in children and adolescents. To date, most studies require that subjects meet criteria for diagnoses, such as conduct disorder (CD), for inclusion in the trials. Although CD includes aggressive behavior, it is also a diagnosis that is problematic and perhaps less than ideal for studies of aggression. Many symptoms of CD—including lying, stealing, truancy, and running away—are unlikely to be affected by drug. Treatment is aimed at reducing aggression, not the other symptoms. Moreover, the overlap between the symptoms of CD and delinquency may lead regulatory agencies to avoid the CD diagnosis in labeling for aggression. A more appropriate diagnosis for aggression studies may be intermittent explosive disorder (IED). Its criteria focus exclusively on impulsive aggression, the real target for these studies. However, IED has received little attention in children, and some question if it can be diagnosed retrospectively in this population. We examined data from our work in aggression to investigate whether IED was co-morbid in our sample, and thus, a possible diagnosis to use in future studies.

Methods: The subjects were 40 children (33 males) between the ages of 9.5 to 15.9 years. All participated in a study of lithium for reducing aggression in CD. Data from the trial were employed to diagnose IED (Coccaro's research criteria) as follows: Criterion A (recurrent aggression) and Criterion B (aggression out of proportion to the provocation) by history; Criterion C (impulsive aggression) using the Child Behavior Checklist; Criterion D (outbursts twice a week) using the Overt Aggression Scale; Criterion E (not better accounted for by another diagnosis) using the Diagnostic Interview for Children and Adolescents; and Criterion F (aggression causing marked distress) using the Clinical Global Impressions.

Results: Ten (25%) of the subjects met all Criteria for IED. The remainder met all criteria for IED, except for Criterion C.

Conclusions: IED is a diagnosis that could be used in aggression treatment studies. All of the above subjects met 4 of 5 criteria for IED-R, i.e. all but Criterion C. However, it is likely they would have met another definition than used above for Criterion C (impulsive aggression) in that they all demonstrated frequent aggressive behavior on the inpatient unit. Thus, with a specific prospective assessment for IED, close to 100% of our subjects would have met criteria for IED. Further assessment of the IED diagnosis is needed.

Session I - 42

Decreased Fluoxetine/Norfluoxetine Plasma Concentration When Used in Conjunction with Naltrexone in Depressed Alcoholics

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Background: Naltrexone is a potentially useful medication in conjunction with fluoxetine to treat alcoholism among patients with major depression. It is unclear, however, whether the combined use of naltrexone and fluoxetine may result in medication interaction. Also, there are no reports examining the serum concentrations of fluoxetine and its active metabolite, norfluoxetine, and their relationship to depressive symptoms and alcohol use among depressed patients with co-occurring alcoholism.

The aim of this study is to examine whether naltrexone impacts on the plasma concentrations of fluoxetine and norfluoxetine, and to explore whether steady state fluoxetine/norfluoxetine plasma concentrations correlate with mood symptoms or alcohol use.

Methods: The sample consisted of 80 subjects (46% females) who completed a clinical trial evaluating the efficacy of fluoxetine (dose range 20-60mg/day± naltrexone hydrochloride [dose 50 mg/day]) in the treatment of major depression with comorbid alcoholism. We used validated chiral methods to measure plasma concentrations for R- & S-Fluoxetine and R- & S-Norfluoxetine in 433 samples.

Results: The results showed that the total fluoxetine+norfluoxetine plasma concentrations over the study period were significantly lower for the naltrexone group (overall mean 153, sd=145) compared to the placebo group (mean 202, sd=197) (t=2.90, df=431, p=.004). The fluoxetine/norfluoxetine plasma concentration significantly discriminated between the treatment groups (F=5.49, df=1, p=.022). The two groups were not statistically different on mean fluoxetine dose received (PBO mean 33.4 (sd=14.8) vs. NTX mean 31.8 (sd=14.9)). Also, they did not differ on several indices of medication adherence. Furthermore, while the S-Norfluoxetine serum concentration significantly negatively correlated with Hamilton depression and anxiety scale scores, the R- & S-Fluoxetine and total fluoxetine concentration significantly negatively correlated with number of drinks per heavy drinking day.

Conclusions: These results provide evidence of potential interaction between naltrexone and fluoxetine, and of potential differential patterns of correlation of S-norfluoxetine and fluoxetine with depressive and alcohol use symptoms.

Session I - 43

The DID Anhedonia Rating Scale:
Results of the First Validation Study

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Background: Anhedonia has been considered to be a core symptom of depression since the term was coined by Ribot in 1896. Conceptually, it has been considered to be a state or personality variable, trait, or symptom, or both. With the advent of diagnostic schedules, inquiry about anhedonia was limited to questions about loss of interest and pleasure associated with specific activities. Anhedonia, per se, was considered a "derivable" variable.

Methods: The Depression Inventory Development group (DID) anhedonia scale assesses eight "domains" of pleasurable experience. An unanchored global anhedonia question was asked at the beginning, and a similar but anchored question was asked at the end of the interview. Interest and pleasure were inquired about separately. The standard used for comparison was the Bech-6 sub-scale (Bech) of the Hamilton Depression Rating Scale (HDRS), which was administered after the anhedonia scale. The questions were asked using a semi-structured interview. Responses were recorded using the GRID format. Item Response Analysis was used to evaluate the responses to each item. The 94 asymptomatic to severely depressed subjects were recruited at five research sites and evaluated by trained interviewers.

Results: The items with the highest correlations with the total Bech score were the anchored global anhedonia items (interest and activity) Accomplishment, Hobbies, Social-Friends, and Social-Family. Each of these items had good discrimination across the range of disease severity. Sensory Experience, Food and Appetite, Sexual Activity, and Spiritual Experience questions were sensitive only at more severe levels of depression. The anchored global item was superior to the unanchored question.

Conclusions: The ability to experience pleasure is a core symptom of depression which is not directly assessed by either the HDRS or Montgomery-Asberg depression rating scales. The neurobiology of depression suggests that there may be an intimate relationship between the disease and both interest and pleasure. We have shown a relationship between depression and anhedonia in eight domains of pleasure, as well as a global item. Four of these items appear to be sensitive across a wide range of severity; four domains appear to be sensitive only in more severe depression. Interest and pleasure do not appear to be independent measures of anhedonia. The addition of an anhedonia item or scale may improve the precision of clinical trial research.

Session I - 44

Signal Detection in Antidepressant Clinical Trials: Can Anything Make a Difference?

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Background: Clinical experience and the bulk of controlled scientific data indicate that antidepressants are effective. However, antidepressant drug effects remain difficult to demonstrate consistently in placebo-controlled clinical trials using traditional methodology; only about half of the trials of known antidepressants demonstrate significant effects.[3] Possible explanations include: 1) Limitations in diagnostic ability such that not all patients entered into clinical trials truly suffer from major depressive disorder per se. It has been hypothesized that such patients might be more likely to respond to placebo quickly. 2) The HAMD may not be the most sensitive instrument for detecting drug placebo differences. One suggestion By Faris and Entsuah[1,2] is that subscales of the HAMD may be more sensitive than the entire scale. 3) Use of analytic methods that do not properly account for the bias from missing data may inflate the rate of false negative results. Several groups[4,5,6] have noted that use of MMRM and other likelihood- or Bayesian-based analyses were preferable to the LOCF analytic approach.

Methods: Data from 11 placebo-controlled trials were used. The first hypothesis was investigated by comparing results from all randomized patients versus results from a "qualified" subset, which had a decrease in HAMD total of <30% during a placebo lead-in phase. The second hypothesis was investigated by comparing mean changes from the HAMD 17-item total score versus subscales of the HAMD. The third hypothesis was investigated by comparing results from the MMRM and LOCF methods.

Results: Using the qualified subgroup did not consistently improve signal detection. All subscales were more sensitive than the HAMD17 total score. MMRM yielded more significant differences from placebo than did LOCF. Use of MMRM and the Maier subscale of the HAMD yielded 16 significant differences in 22 comparisons. Given the powering of these comparisons, the expected number of significant differences was 17.

Conclusions: No evidence was found to support excluding early placebo responders from analyses of antidepressant clinical trials. However, use of MMRM in conjunction with subscales of the HAMD improved detection and yielded a rate of significant differences close to the expected rate.

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Session I - 45

A Randomized, Double-Blind, Placebo-Controlled Trial of Methylphenidate Extended Release (OROS MPH) in the Treatment of Antidepressant-Related Sexual Dysfunction

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Objective: There are limited data to indicate effective treatment strategies for antidepressant-related sexual dysfunction. We studied whether augmentation with methylphenidate extended release (OROS MPH) improved sexual dysfunction associated with antidepressants in patients with treatment resistant major depression (TRD).

Methods: Sixty TRD subjects were enrolled in a 4-week double-blind, placebo-controlled trial of OROS MPH (18 mg - 54 mg/day). The preexisting antidepressants were kept unchanged. The primary efficacy measure was the change in Arizona Sexual Experiences Survey (ASEX) from baseline to end of treatment in an ITT with LOCF approach. Higher ASEX scores represent increased level of sexual dysfunction.

Results: More than 80% (83.3%) of subjects completed the study. The mean dose of OROS MPH was 34.2 mg/day. The mean ASEX scores at baseline did not differ in the two groups (drug=22.4, placebo=23.5). There were no significant differences between the two groups in terms of changes in ASEX scores over time ($F_{(1, 35)} = 1.14$, $p = 0.32$), although the numerical decrease in ASEX score was greater in OROS MPH (mean change=-4.5, 20.1% decrease) than in the placebo group (mean change=-0.6, 2.6% decrease). There was no correlation between improvement in HAM-D and ASEX scores. Combination of OROS MPH and antidepressants was well tolerated.

Conclusions: Augmentation with OROS MPH showed no statistically significant benefit in antidepressant-related sexual dysfunction. Addition of OROS MPH to antidepressants did not worsen preexisting sexual dysfunction. The negative findings should be interpreted in the context of a lack of power, short trial period, and resistant nature of depression. Adequately powered, controlled trials are needed to fully evaluate the efficacy of OROS MPH in this area.

Session I - 46

A Randomized, Placebo-Controlled Trial of Risperidone Augmentation for Patients with Difficult-To-Treat Unipolar, Nonpsychotic Major Depression

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Background: In patients with major depression, 30%-50% do not remit despite an adequate trial of antidepressant pharmacotherapy. This double-blind placebo controlled study evaluated the use of risperidone as an augmenting agent for patients who showed an incomplete response to an antidepressant.

Methods: Patients were enrolled if they (1) met criteria for unipolar nonpsychotic major depression, assessed with the Structured Clinical Instrument for DSM-IV, (2) had completed an adequate trial of open-label antidepressant medication for 5 weeks, and (3) showed no response or only partial response, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) score $\geq$ 15. Between two sites, 97 subjects were randomly assigned in a 2:1 ratio to receive double-blind treatment with adjunctive risperidone (0.5 mg to 3 mg per day) or placebo for 4 weeks, in conjunction with the same open-label antidepressant at the same dose. The primary outcome was remission, defined as a MADRS score $\leq$ 10. Secondary outcomes included remission defined as Hamilton Rating Scale for Depression (HRSD) scores $\leq$ 7, Clinical Global Impression (CGI) ratings, adverse events, and quality-of-life ratings (Q-LES-Q). Modified intent-to-treat analyses included all subjects who received at least one dose of study medication.

Results: Mean (SD) baseline scores on the MADRS for subjects assigned risperidone were 25.8 (5.7), and for those assigned placebo were 25.5 (5.4) (t[95] = -0.25, p = 0.99). MADRS scores for subjects in both treatment groups improved significantly, but the odds of remitting were significantly better for subjects receiving risperidone (odds ratio = 3.33, 95% CI = 1.30-8.53, p = 0.011). In the risperidone augmentation group, 51.6% (32/62) remitted, compared to 24.2% (8/33) of the placebo augmentation group (Cochran-Mantel-Haenszel[1] = 6.48, p = 0.011). Remission as defined by HRSD scores showed that 35.5% (22/62) of the risperidone augmentation group remitted compared to 18.2% (6/33) of the placebo group (Cochran-Mantel-Haenszel [1] = 3.10, p = 0.078). CGI scores improved for both treatment groups (risperidone 4.2 to 2.8, placebo 4.1 to 3.2; F[1,91] = 2.92, p = 0.091). Of the subjects receiving risperidone, 84.4% (54/64) reported at least one adverse event, compared to 81.8% (27/33) of the subjects receiving placebo (X^2(1) = 0.10, p = 0.75). Q-LES-Q ratings of quality-of-life were significantly better for subjects receiving risperidone compared to those receiving placebo (risperidone group improved from 1.3 to 2.5, placebo group improved from 1.2 to 1.7; F[1,62] = 6.44, p = 0.014).

Conclusions: For patients with difficult-to-treat depression, augmenting an antidepressant with risperidone leads to a significantly higher rate of remission and a significantly better quality of life, without an increase in overall side effect burden.

Session I - 47

Impact of Duloxetine Treatment on Plasma Norepinephrine and Dihydroxyphenylethylene Glycol in Depressed Patients

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Background: Duloxetine inhibits the reuptake of norepinephrine (NE) and serotonin, and these pharmacodynamic effects are presumed to explain its established efficacy as an antidepressant. Reduced NE reuptake into neurons may manifest as a decrease in the deaminated metabolite dihydroxyphenylethylene glycol (DHPG) measured in the periphery.[1,2] To date, however, the effects of duloxetine on catecholamines have only been reported in healthy volunteers. We report here on a study in depressed outpatients treated with duloxetine (DLX) or placebo (PLA) in which heart rate (HR), blood pressure (BP), plasma NE, and plasma DHPG were measured in supine and standing positions, both prior to the initiation of and during treatment.

Methods: Some details and results of study H8I-MC-HQAC have been previously presented.[3] Thirty-five patients were randomized to DLX (at a dose of either 60 mg QAM or 60 mg BID) and 35 were randomized to PLA. At each of visits 1, 5, and 6, patients underwent a "posture test": Patients were supine for 10 to 30 minutes until consecutive HR measurements 5 minutes apart differed by (3 beats/min, then supine HR and BP were measured, and then samples for supine NE and DHPG were collected; patients then stood upright for 10 minutes, then standing HR and BP were measured; and then samples for standing NE and DHPG were collected.

Results: Baseline (Visit 1) values of HR, BP, NE, and DHPG were comparable in the DLX and PLA arms. The reproducibility of DHPG values during treatment (Visits 5 and 6) was high as determined using the Concordance Correlation Coefficient (CCC): supine DHPG=0.637, standing DHPG=0.621. Reproducibility was lower for NE values during treatment (CCC: supine NE=0.431, standing NE=0.371). In changes from baseline to Visit 5 and to Visit 6, both supine and standing DHPG levels demonstrated statistically significant decreases in DLX patients compared to PLA patients (supine: $p<0.01$, standing: $p< 0.01$). Trends in systolic BP (increased in DLX patients) and supine NE (decreased in DLX patients) were seen but did not achieve statistical significance.

Conclusions: The decrease in DHPG observed in depressed patients treated with duloxetine is consistent with results previously reported in healthy volunteers, and suggests that duloxetine is acting as a norepinephrine reuptake inhibitor at the doses tested. This pharmacodynamic effect may be contributing to the efficacy of duloxetine as an antidepressant.

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Session I - 48

Can MADRS Replace CDRS-R in Adolescent Depression Trials?

Shailesh Jain, M.D., M.P.H. [1], Thomas Carmody, Ph.D. [1], Madhukar H. Trivedi, M.D. [1], Carroll W. Hughes, Ph.D. [1], Ira Burnstein, Ph.D. [2], David W. Morris, Ph.D. [1], Taryn Mayes, M.S. [1], Graham Emslie, M.D. [1], A. John Rush, M.D. [1]

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Objective: The purpose of this study is to compare the psychometric properties of the Child Depression Rating Scale-Revised CDRS-R) and the Montgomery Asberg Depression Rating Scale (MADRS) in children and adolescents with major depressive disorder (MDD).

Background: CDRS-R, a commonly used measure, is time consuming to administer and requires extensive training. The MADRS, a familiar adult symptom measure, is shorter, but lacks psychometric data in children and adolescents with depression. To our knowledge, no comparative analyses of the CDRS-R and the MADRS have been performed in these patient populations.

Methods: Symptom ratings based on the CDRS-R and the MADRS were obtained from outpatient children (n=96, 8-11 years) and adolescents (n=123, ages 12-18 inclusive), with non-psychotic MDD who participated in a randomized placebo controlled trial of fluoxetine (titrated to 20 mg/day and continued for 8 weeks after 10 mg/day for one week). Symptoms were rated with the CDRS-R and MADRS with input from parents. Analyses were conducted using Classical Test Theory and Item Response Theory methods.

Results: The total score correlation between MADRS and CDRS-R at baseline and exit was 0.51 and 0.85 (children) and 0.66 and 0.85 (adolescent), respectively. The Cronbach's alpha at exit for CDRS-R was 0.86 (children) and 0.91 (adolescent). The Cronbach's alpha at exit for MADRS was 0.82 (children) and 0.88 (adolescent). The effect sizes for change from baseline to exit between the fluoxetine and placebo groups for the CDRS-R was 0.78 (children) and 0.38 (adolescents), and that for the MADRS. 0.61 (children) and 0.15 (adolescents). Agreement between the CDRS-R and MADRS in the assessment of treatment response (50% improvement from baseline) occurred in 84.2% of children and 79% of adolescents. Test information functions for both scales differed significantly in children only with the CDRS-R showing greater precision.

Conclusions: In this study, the CDRS-R performed better than the MADRS in distinguishing drug from placebo. Whether CDRS-R can be shortened while retaining its sensitivity to change will be discussed.

Poster # I - 49 was not presented at the meeting.

Session I - 50

Diurnal Mood Variation in Outpatients with Major Depressive Disorder: Implications for DSM-V

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Objective: Diurnal mood variation with early morning worsening is included as a cardinal feature of Melancholic subtype of major depressive disorder (MDD), in both the DSM and ICD classifications. We examined the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study baseline data to determine whether diurnal mood variation with morning worsening, as well as with afternoon and evening worsening of mood, were related to other symptom constructs.

Methods: Outpatients with nonpsychotic MDD (n=3744) recruited by 41 clinical sites throughout the United States for participation in the STAR*D study were included for this report. Baseline demographic and clinical features, including specific symptoms, were evaluated. The Inventory of Depressive Symptomatology-Clinician-rated was used to assess the presence and type (occurrence in morning, afternoon, or evening) of diurnal mood variation, and its relationship to environmental events, as well as melancholic and other symptoms.

Results: Diurnal mood variation was reported by 22.4% (n=837) of the total sample; however, only 3.3% (n=28) of the 837 patients with diurnal variation attributed the diurnal variation to environmental factors. Of the 809 patients with diurnal mood variation unrelated to environmental events, 31.9% (n=258) reported morning worsening, while 19.5% (n=158) and 48.6% (n=393) reported afternoon and evening worsening, respectively. Minimal distinctions in demographic characteristics, clinical features, and depressive symptoms were found between patients with morning worsening and those with either afternoon or evening worsening. Surprisingly, other melancholic symptom features (i.e. distinct quality of mood, psychomotor slowing) were associated with diurnal mood variation regardless of time of day (e.g. morning, afternoon, or evening diurnal mood worsening).

Conclusions: These results suggest that the DSM definition of melancholic features might be revised to include morning, afternoon, or evening diurnal mood worsening.

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Signal Detection Properties of Four Outcome Scales in Clinical Trials in Patients with Major Depressive Disorder

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Objective: In intervention studies in patients with major depressive disorder (MDD), disease specific outcomes are commonly measured by the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery Asberg Depression Scale (MADRS), and overall changes are measured by the Clinician Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I). In this analysis, we examined signal detection properties of these scales in a large MDD clinical trial dataset.

Methods: Data from 22 randomized, double-blind, placebo-controlled venlafaxine extended release (XR) and venlafaxine immediate release (IR) studies (10 XR studies, 11 IR studies, 1 with both formulations) in adult patients with MDD were pooled and examined from baseline through the end of treatment for each individual study (most studies were short-term). Signal detection characteristics were evaluated for the four scales using both continuous and binary outcomes, examining post-hoc alpha ("p-values"), beta error estimates ("power"), and effect sizes of venlafaxine vs placebo. Binary outcome improvement (or "response") was defined as 50% or greater change in the HAM-D or MADRS, and a score of 2 or less on the CGI-S and CGI-I.

Results: For continuous outcomes at the 0.05 level, differences in change scores between venlafaxine and placebo reached statistical significance in 16 studies for the CGI-I and MADRS, 15 studies for the HAM-D, and 14 studies for the CGI-S. Power was 80% or higher in 13 studies for the CGI-I, 12 studies for the CGI-S and HAM-D, and 11 studies for the MADRS. Pooled effect sizes ranged from 0.38 on the HAM-D to 0.42 on the MADRS for continuous variables. For binary outcomes, pooled effect sizes ranged from .31(CGI-S) to .41(CGI-I). Outcomes in 20 of 22 studies were concordant (defined as 6 of 8 outcome measures being significant or 6 of 8 being not significant). All individual items on the HAM-D and MADRS were significantly correlated when studies were pooled.

Conclusions: The four outcome scales generally produced similar results. Continuous outcomes provided larger effect sizes. Within individual studies, outcomes tended to be concordant.

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Evaluating the Maintenance Effect of Duloxetine in Patients with Major Depressive Disorder

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Background: A study was designed to evaluate the maintenance effect of duloxetine, defined as longer time to relapse compared with placebo, in patients who received open-label duloxetine 60 mg QD during a 12-week lead-in phase, met randomization criteria (defined as meeting the following at both Weeks 10 and 12: $HAMD_{17}$ ≤ 9, CGI-Severity ≤ 2, and not meeting DSM-IV criteria for major depressive episode), and were randomly assigned to duloxetine 60 mg QD or placebo during a 26-week double-blind continuation phase.

Due to comments from the FDA that maintenance language in the label should be associated with the observed length of response in the lead-in phase, we conducted ad hoc analyses of time to relapse in the subsets of patients who demonstrated different durations of continuous response.

Methods: The protocol defined response during the lead-in phase as $\geq 50\%$ reduction in the $HAMD_{17}$ from baseline. Ad hoc analyses of time to relapse were performed in patients with 10, 8, and 5 weeks of continuous response prior to randomization.

We performed sensitivity analyses to address the adequacy of the normal approximation, due to the small number of relapses in the 10-week continuous responders, and the effect of discontinuations in the calculation of the p-values for the log-rank test and the log-rank test stratified by country. Therefore, we calculated exact p-values for these two tests, and performed worst-case analyses in which patients who discontinued early were considered as having relapsed.

Results: A total of 278 patients entered the continuation phase. The numbers of patients with 10-, 8-, and 5-weeks of continuous response and with relapse data were 103, 178, and 238, respectively. Results showed statistically significantly longer time to relapse for duloxetine versus placebo in the continuation phase for all randomized patients and those with 10, 8, and 5 weeks of continuous response in the lead-in phase, using the log-rank test and the log rank test stratified by country.

The exact and normal approximation p-values rounded to three decimal places were the same.

When considering early discontinuations as relapses, the results were consistent.

Conclusions: Results showed that duloxetine demonstrated maintenance of effect for 10 weeks in the treatment of MDD using the evaluation method required by the FDA to support a maintenance effect in the label. Sensitivity analyses supported these results.

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Assessing Long-Term Antidepressant Efficacy: A Case Study Comparing a Randomized Withdrawal Trial and a Double-Blind Long-Term Trial

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Introduction: Assessing maintenance of acute efficacy in psychiatric drugs involves a number of complex questions, and the priority of these questions is different for different disorders and for different stakeholders. The present study highlights the attributes of the randomized withdrawal (RW) and double-blind long-term efficacy (DBLE) designs.

Methods: In the RW study, adult outpatients with MDD received the experimental drug for 12 weeks (N=533). Patients meeting criteria for adequate response were then randomized to continue on the same dose of drug (N=136) or placebo (N=142) for 26 weeks. The primary analysis was based on time to relapse, with secondary analyses including mean changes over time. In the DBLE trial, acute treatment included two identical multi-site, randomized, double-blind, placebo- and active comparator-controlled studies with a duration of 8 weeks using two doses of the same drug as described previously for the RW trial. Patients who had a >/=30% reduction from baseline in HAMD17 total score at the end of the acute phase were allowed to continue on the same (blinded) treatment during the continuation phase. Efficacy valuations were based on all randomized patients, with the primary analysis based on a binary endpoint (success/failure), with success defined as completing the trial and being in sustained remission at least the last 3 months. Secondary analyses included mean changes and alternative definitions of sustained remission.

Results: In the RW trial, time to relapse was significantly longer for drug compared with placebo. With approximately the same number of patients and exposure to placebo, the DBLT design provided substantial evidence of efficacy for two doses during acute treatment, in that both doses separated significantly from placebo in both acute phase studies. The DBLE design also yielded definitive evidence of long-term efficacy and provided more interpretable safety assessments than the RW design.

Conclusions: The DBLE design may be a useful approach for assessing long-term risk vs. benefit.

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Combination Cognitive Behavior Therapy and Pharmacotherapy Versus Pharmacotherapy Alone: A Meta-Analysis of Effect in the Published Randomized Clinical Trials

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Background: Despite much intuitive support, the advantage of routinely combining cognitive behavior therapy (CBT) and medication for the treatment of major depression remains a controversial topic. The acute phase monotherapy studies of CBT and pharmacotherapy have established efficacy. The failure to show an additive benefit of combination treatment in small, randomized clinical trials (RCT) does not necessarily mean that there is no advantage in combining treatments.

Objective: To examine the efficacy of cognitive behavior therapies, including the model of Beck (1979) and colleagues, and related interventions, such as McCullough's Cognitive-Behvaior Analystic System of Psychotherapy (2000), in combination with medications as compared to pharmacotherapy alone in the relevant, published RCTs.

Methods: We used meta-analysis to estimate the effect of CBT in combination with pharmacotherapy compared to pharmacotherapy alone. For each study individually, and overall, random effects pooled estimates of odds ratios, and corresponding 95% confidence interval of the rate differences were computed. Estimates were compared using the chi-square statistic. The results are represented in a forest plot summarizing the meta-analysis of response to combined therapy compared to pharmacotherapy alone. All statistical analyses were performed with the SAS statistical package.

Results: Although the Keller et al. study was the only study to observe a significant advantage favoring combined treatment, each of the other studies yielded odds ratios that were quite similar to the Keller et al. results. The major difference is not the magnitude of the advantage for combined therapy, but rather the wider confidence intervals of the smaller studies. This suggests that adding CBT to pharmacotherapy may increase the likelihood of response by a magnitude as large as 20; therein, for every five patients treated, using combination therapy would produce one more responder. The odds ratio calculated by combining the five studies favors combination therapy over pharmacotherapy ($P = .0001$).

Conclusions: While it is important that null results prohibit a definitive conclusion, it is possible that Type Two Error (i.e., a "false negative" conclusion resulting from inadequate power to detect a modest difference) is the consequence of small sample size. Four of five RCTs comparing combination CBT and pharmacotherapy and pharmacotherapy alone do suffer from the problem of small sample size; nonetheless, meta-analysis produced similar effect sizes to the adequately sized Keller et al. study.

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Does Class of Antidepressant Drug Resistance Predict Outcome to Treatment with Electroconvulsive Treatment for Major Depression?

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Background: Approximately 85% of patients treated with electroconvulsive therapy (ECT) are in a major depressive episode, either unipolar or bipolar, and, by far, lack of sufficient benefit from adequate antidepressant treatment is the most frequently cited indication for ECT. The impact of antidepressant resistance on outcome with ECT has most frequently been examined by considering antidepressant drugs generally rather than by class. This study examines whether specific classes of antidepressant medications differ in their predictive relationships to short-term ECT outcome and relapse.

Methods: Ninety patients with major depressive episode and a pretreatment Hamilton Rating Scale for Depression (24 item) of >18 participated in a study of the effects of pulse width and electrode placement on the efficacy and cognitive effects of ECT. Class, strength, number, and duration of antidepressant medication trials were rated using the Antidepressant Treatment History Form. Classes of antidepressants were defined as: cyclic antidepressants, specific serotonin reuptake inhibitors, specific norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and other antidepressant medications. A masked clinical evaluation team completed HRSD ratings before, twice weekly, and within two days of the completion of ECT, and one week later. Remission was defined as a HRSD score $\leq$10 one-week following ECT. Remitters were followed for one year or until relapse. Relapse was defined by hospitalization, suicide attempt, emergence of psychotic depression, or a substantial increase in HRSD score ($\geq$ 16).

Results: In bivariate logistic regression analyses, higher scores for trial adequacy were significantly associated with lower rates of remission following ECT for the TCA, MAOI, and Other Antidepressant classes of treatment, while adequacy of SSRI or SNRI classes were not predictive of outcome. In a simultaneous logistic regression with these five classes, age, and preECT HRSD score as predictors, only the potency of MAOI and Other Antidepressant trials were significant predictors of ECT short-term outcome. Sixty-eight remitters were monitored for relapse. A parametric survival analysis on time to relapse indicated that potency of the strongest MAOI and Other Antidepressant trial had powerful relations with time to relapse, while there was a trend for the TCA class, and no effect for the SSRI or SNRI categories. More potent MAOI, TCA, and other antidepressant trials were associated with higher rates of relapse.

Conclusions: These findings indicate that adequacy of MAOI and TCA trials has lawful relationship to ECT outcome and to relapse following ECT. In contrast, such predictive relations are not seen with SSRI or SNRI medications.

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The Number Needed to Treat — A Useful Measure of Treatment Effect: Lessons Learned from Studies of Preventative Treatment in Seasonal Affective Disorder

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Background: When reviewing results of clinical trials, it is important to evaluate the relative risks and benefits of treatment. The number needed to treat (NNT), defined as the number of patients who need to be treated to prevent one additional illness, has been proposed by some authors to be easier to interpret and more clinically meaningful than other measures of risk (e.g., relative risk, odds ratio) typically used in clinical trials. It has also been advocated that NNT become a standard part of clinical trial reporting.

Methods: NNTs were calculated for three placebo-controlled trials designed to evaluate the safety and efficacy of bupropion XL (Wellbutrin XL®) for prevention of seasonal major depressive episodes in patients with a history of seasonal affective disorder (SAD). These three trials were conducted across two autumn-winter seasons (2002-2003 and 2003-2004) in 1042 outpatients who were enrolled in the autumn, prior to the onset of a seasonal depressive episode. Patients received matching placebo or bupropion XL at a target dose of 300 mg/day until the conclusion of treatment in early spring. NNTs were derived from depression-free rates at end of treatment. For the purpose of comparison, NNTs were also calculated for other accepted medical and psychiatric preventative treatments. Data used to calculate NNTs for products not marketed by GlaxoSmithKline were collected via MEDLINE search.

Results: The number of patients needed to treat to obtain one patient who would benefit from treatment (i.e., remain depression-free throughout the study) was 7-10 across the three SAD studies. These NNTs are more favorable than from many approved and widely accepted preventative treatments (e.g., aspirin for prevention of myocardial infarction = 111, lovastatin for prevention of first coronary event in patients with low high-density lipoprotein cholesterol levels = 50), less favorable than one (pneumococcal vaccine = 5), and comparable to NNTs observed in relapse studies of depression and bipolar disorder (NNT = 3-20).

Conclusions: NNT provides a clinically meaningful way to evaluate treatment effect in clinical trials. Preventative treatment of seasonal depressive episodes with bupropion XL yielded NNTs that were more favorable than those of many preventative medical therapies and comparable to those observed in psychiatric relapse prevention studies.

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Site vs. Centralized Raters in a Clinical Depression Trial

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Objective: The use of triple-blinding procedures, where raters are blind to study visit and design, has been suggested as a way to improve rating fidelity. Several studies have shown that using different raters at baseline and endpoint improves signal detection. The use of centralized raters, who are linked to study sites and interview patients via two-way videoconferencing, has been proposed as a means to achieve such blinding. The current study compared site and centralized ratings in a two-center depression trial.

Methods: Patients were interviewed twice at each of three time points: screening, baseline, and endpoint, once by the site rater and once remotely via videoconference by a centralized rater, who was blind to study visit and design. Raters were blind to each others' scores. A counter-balanced order was used at baseline and endpoint. A site HAMD score of 17 or greater was required for study entry at both screening and baseline visits.

Results: Site HAMD scores were significantly higher than centralized raters scores at screening and baseline, but not at endpoint. Correlations (ICC) between site and centralized ratings at screen and baseline were .33 and .40, but improved to .75 at endpoint. Internal consistency reliabilities (coefficient alpha) for centralized ratings were .71, .79, and .84 at screen, baseline, and endpoint, and .31, .39, and .83 for site raters, respectively. Forty-three percent of patients found eligible at screen by site raters were found ineligible by centralized raters, and 57% of patients found eligible at baseline were found ineligible by centralized raters.

MEAN HAMD SCORE BY VISIT			
	Screen (n=32)	Baseline (n=27)	Endpoint (n=22)
Central Raters	16.28	14.26	11.68
Site Raters	19.88	18.85	11.78
DIFF	**3.59**	**4.59**	**0.05**
P value	.0001	.0001	.968

Internal Consistency Reliability (coefficient alpha)			
	Screen	Base-line	End point
Cent, Raters	.71	.79	.84
Site Raters	.31	.39	.83

Conclusions: The use of blinded raters would result in significantly different study populations. Blinded raters generally score depression severity lower at screen and baseline. Site and centralized ratings coalesced at endpoint. Results support previous findings comparing site and self-report ratings.

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Quetiapine Augmentation for Treatment-Resistant Depression

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Objective: Growing evidence supports augmentation of antidepressant therapy with atypical antipsychotics in treatment-resistant depression.[1,2] This study investigated augmenting concurrent treatment with quetiapine in depressed patients partially responsive to SSRI/SNRI treatment.

Methods: In this 8-week, double-blind, placebo-controlled trial, patients (18-65 years) with baseline HAM-D$_{17}$ scores $\geq$20 following 8 weeks of SSRI/SNRI treatment were randomized to receive quetiapine (200-400 mg) or placebo as augmentation to SSRI/SNRI treatment. Efficacy measures included HAM-D$_{17}$, MADRS, CGI-S, and CGI-I at study end.

Results: Baseline HAM-D$_{17}$ scores were 25.0 and 24.5, and baseline MADRS scores were 32.5 and 33.5, for quetiapine (mean dose 268 mg/day, n=21) and placebo (n=11), respectively. Following treatment, patients receiving quetiapine had significantly lower HAM-D$_{17}$ scores versus placebo (8.3 versus 14.7, respectively, p<0.01). More patients receiving quetiapine responded to treatment ($\geq$50% reduction in HAM-D$_{17}$ score) (67% versus 27%, p=0.015), and achieved remission (HAM-D$_{17}$ score <7) (43% versus 15%, p<0.05), versus placebo. Patients receiving quetiapine had significantly lower MADRS (15.4 versus 24.8, p<0.02), CGI-S (3.0 versus 4.0, p<0.03) and CGI-I (2.6 versus 3.5, p<0.04) scores versus placebo. Quetiapine treatment was generally well tolerated.

Conclusions: Quetiapine augmentation of SSRI/SNRI treatment may benefit patients with treatment-resistant depression and warrants further investigation.

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Session I - 59

Midline and Right Frontal Brain Function and Remission in Major Depression

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Background: Prior investigations have reported that EEG changes may have use as a biomarker of clinical response to antidepressant medication,[1,3] because physiologic changes precede significant symptom improvement. Achieving remission has been identified as a more meaningful outcome measure in recent clinical research. In addition, these past studies used a neuroanatomically defined prefrontal region of interest. Using cluster analysis to examine changes in QEEG cordance[4] in healthy volunteers taking antidepressants, we derived a new, lateralized region of interest using electrodes overlying midline and right frontal cortical areas (FPz, Fz, FP2, AF2, F4, F8 electrodes). Here we evaluated the relationship between early decreases in theta-band cordance in this MFRC region and remission in depressed patients.

Methods: Subjects were adult outpatients with unipolar major depression who participated in a placebo-controlled antidepressant treatment trial in our lab (entry Ham-D$_{17}$ > 17), had been assigned to receive medication (fluoxetine n=13, venlafaxine n=24), and completed one of these 8 week trials; in all, we examined data on 37 subjects (mean age 42.7 + 12.3 years; 62.2% female). Age, gender, and intake symptom severity did not differ significantly among trial groups. We used logistic regression to assess changes in theta-band cordance in the MRFC region at 48 hours, 1 week, and 2 weeks after start of drug as predictors of remission (final/week 8 Ham-D$_{17}$ < 5).

Results: Overall, 11 of 37 subjects (30%) remitted. Change in MRFC 1 week after start of drug was significantly associated with remission (coefficient = -1.08, SE = .50, exact p = .02. At two weeks, change in MRFC showed a statistical trend in the same direction (coefficient = -1.05, SE = .60, exact p = .06). Receiver Operating Characteristic (ROC) analysis of the one-week MRFC predictor yielded .73 area under the curve. Using a cutpoint of 0, decreases in MRFC predicted remission with 68% overall accuracy (90% sensitivity; 58% specificity).

Conclusions: These results expand prior findings of EEG changes that precede symptomatic response to antidepressant treatment, by focusing on remission as the salient clinical endpoint and using a right-lateralized region of interest derived from physiologic findings. They suggest that remission with antidepressant medications may be predictable from physiologic measurements after 1 week of treatment. We will be able prospectively to test the reliability, reproducibility, and generalizability of this potential biomarker of remission in data being collected in an ongoing collaborative treatment trial at UCLA and Massachusetts General Hospital (R01MH069217 (Cook) and R01MH069180 (Alpert)).

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Session I - 60

The Delusional Assessment Scale for Psychotic Major Depression: Reliability, Validity, and Utility

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Background: Delusions are the hallmark of major depression with psychotic features (MDPsy). Nevertheless, a scale that reliably measures the intensity of beliefs across multiple delusional domains has been not been previously available. The Delusional Assessment Scale (DAS) was developed to assess the characteristics of delusions among patients with MDPsy, determine how the nature of delusions among older patients differ from those in young adults, and compare delusions in MDpsy with those in patients with schizophrenia.

Methods: Scale items were selected based on previous studies of delusional ideation in schizophrenia. Anchor points and rating instructions were developed. A three-point item to assess mood congruence was added. Following reliability assessment, the 15-item scale was administered to subjects participating in the four-site collaborative Study of the Pharmacotherapy of Psychotic Depression (STOP-PD). Factor analyses were carried out followed by an assessment of the internal consistency identified factors. The scale was then validated against specific items from the Brief Psychiatric Rating Scale (BPRS). Data from the first 130 subjects in the STOP-PD trial were analyzed to determine relationships between older age and scores on DAS factors.

Results: Inter-rater reliability revealed an I.C.C. of >.76 for all of the 15 scale items. Principal Components analysis demonstrated that the data were best fit by a five-factor model, (impact, conviction, disorganization, bizarreness, and extension). Scores on specific domains were significantly correlated with the BPRS unusual thought content and positive symptom scores, but were not related to BPRS depression item. A comparison between young adult and geriatric patients revealed that delusions had a greater impact in older patients, while men demonstrated greater conviction, regardless of age.

Conclusions: The DAS is a reliable and valid 15-item measure of five delusional domains that distinguishes delusions in young patients with MDPsy from those of older adults.

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Single-Center, Placebo-Controlled, Flexible-Dose, 12-Week Study of Paroxetine in the Treatment of Dysthymic Disorder Without Major Depression

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Background: There are no previously published placebo-controlled studies of the effectiveness of paroxetine treatment in patients with dysthymic disorder without comorbid major depression.

Methods: Forty-five patients with a diagnosis of DSM-IV dysthymic disorder, without major depression, were studied in this 12-week, double-blind, randomized, placebo-controlled design. After a 1-week single-blind placebo lead-in, patients were randomly assigned to either placebo (N=22) or flexible doses (20-40 mg/day) of paroxetine (N=23). Outcome measures included the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions – Severity (CGI-S), – Improvement (CGI-I), Cornell Dysthymic Rating Scale (CDRS), and the Beck Depression Inventory (BDI).

Results: Analyses were completed on the mean change scores for all outcome measures in an intent-to-treat population (N=40). In comparison with the placebo group, the paroxetine group showed a greater reduction in both the CGI-S scores (p=.05) and CGI-I scores (p=.01) at endpoint. Significantly greater endpoint improvement with paroxetine than placebo was also obtained for the BDI (p=.03). While the MADRS and HAM-D 29 did not reveal significant differences, trends were observed in both the HAMD-17 (p=.089) and the CDRS (p=.07). The proportion of responders (defined for HAM-D and MADRS scores as a 50% reduction and for CGI-I as a score of 1 or 2 by the final visit) and remitters (HAMD-17 score of less than or equal to 8) were significantly higher for the paroxetine group relative to the placebo group (p=.01, p<.01, respectively). Significantly greater improvement in quality of life was seen with placebo versus paroxetine (p<.01) on the Quality of Life Enjoyment and Satisfaction Questionnaire. Adverse experiences reported by three or more subjects in the paroxetine group included nausea (28.6%), headache (33.3%), sexual dysfunction (23.8%), diarrhea (14.3%), fatigue (14.3%), and sweating (14.3%). In the placebo group, nausea (21.0%) and headache (15.8%) were reported. Twelve patients dropped out before completion of the study (paroxetine N=5, placebo N=7); the main reasons reported within the paroxetine group were adverse experiences (N=3), and lack of efficacy in the placebo group (N=5).

Conclusions: Paroxetine is well tolerated and efficacious in reducing symptoms and improving quality of life in the short-term treatment of dysthymic disorder without comorbid major depression.

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A Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Trial of Augmentation with OROS Methylphenidate in Treatment-Resistant Depression

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Background: In the first randomized, double-blind, placebo-controlled trial (RCT) of stimulant augmentation in treatment resistant depression (TRD), we examined the efficacy and safety of augmenting with OROS methylphenidate (MPH) for non-or partial responders to antidepressants.

Methods: Sixty subjects with TRD were enrolled in a 4-week RCT of OROS MPH (18 mg to 54 mg per day). The preexisting antidepressant dose was kept unchanged. The primary efficacy measure was a change in scores on the Hamilton Depression Rating Scale-21 items (HAM-D) from randomization to end of treatment. Secondary efficacy measures included changes in Clinical Global Impression-Improvement (CGI-I) and severity (CGI-S). Treatment response was defined as a 50% reduction in HAM-D or end of treatment CGI-I of 1 or 2.

Results: 83% of subjects completed the study. The mean dose of methylphenidate ER was 34.2 mg/day. ITT analyses found no statistically significant differences between OROS MPH (n=30) and placebo (n=30) in reduction in HAM-D (-6.9 in drug and -4.7 in placebo). ($F(1,47)=1.24$, $p =.22$). Although there were numerically more responders in the drug group (40% by HAM-D, 43.3% by CGI-I) versus the placebo group (23.3% by HAM-D, 26.6% by CGI-I), this did not reach statistical significance. OROS MPH was well tolerated.

Conclusions: The study failed to show a statistically significant benefit for augmentation with OROS MPH in patients with TRD. Possible explanations for the negative findings include inadequate power, suboptimal dosing, and failure to account for comorbid ADHD. Adequately powered RCT with comorbid ADHD as a stratifying variable are necessary to fully evaluate the efficacy of OROS MPH in treatment-resistant depression.

Session I - 63

Construction and Initial Validation of an Instrument to Assess Subjective Expectations of Depression Treatment in Clinical Trials: The Response Expectancy Questionnaire

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Background: Randomized, controlled clinical trials (RCTs) are considered the gold standard for evaluation of new antidepressant therapies. High placebo response rates are a well-known confounder in depression trials, with up to 50% of all RCTs failing due to high placebo response rates.[1] Patient expectations have been found to be a significant predictor of treatment outcomes.[2,3] Due to the theoretical link between expectations and treatment outcomes, [2,3] the objective of this project was to develop and conduct preliminary validations of an instrument assessing patient expectations in depression treatment trials.

Methods: Initial items for the Response Expectancy Questionnaire (REQ) were developed by the authors and modified based on an expert consensus panel. The panel consisted of experts in response expectancy, depression trials, and psychometrics. The content validity index (CVI) was based on ratings of relevance of an item to response expectancy theory.

Results: The final draft REQ consists of 23 items across four domains deemed most relevant by the expert panel (perceptions about getting better, likelihood of getting study medication, power of study medication/procedures, optimism and compliance). The final REQ demonstrated a content validity index of 0.945, which indicated that there was excellent agreement on the relevance of each of the items.

Conclusions: A test instrument has been developed to assess multiple aspects of expectancy, as it may relate to placebo responsiveness in trials on affective disorders. A validated instrument like the REQ may help to more efficiently conduct depression trials.

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Session I - 64

Preventing Recurrence of Depression: A Placebo-Controlled Trial of Venlafaxine XR in Patients with Recurrent Unipolar Major Depression

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Background: We report the results of the first 12 months of a 2-year maintenance phase of a study to evaluate long-term efficacy and safety of venlafaxine extended release (XR) in preventing recurrence of depression.

Methods: Patients with recurrent unipolar depression (N=1096) were randomly assigned in a 3:1 ratio to 10-week treatment with venlafaxine XR (75-300 mg/day) or fluoxetine (20-60 mg/day). Responders (HAM-D$_{17}$ total score ≤12 and ≥50% decrease from baseline) entered a 6-month, double-blind continuation phase on the same medication. Continuation phase responders enrolled into the maintenance treatment period consisting of two consecutive 12-month phases. At the start of each maintenance phase, venlafaxine XR responders were randomly assigned to receive double-blind treatment with venlafaxine XR or placebo, and fluoxetine responders were continued for each period. We compared the time to recurrence of depression with venlafaxine XR versus placebo. The primary definition of recurrence: HAM-D$_{17}$ total score >12 and <50% reduction from baseline (acute phase) HAM-D$_{17}$.

Results: Patients responding to venlafaxine XR at the end of continuation phase were randomly assigned to venlafaxine XR (n=164) or placebo (n=172) for the first 12-month maintenance phase; 129 patients in each group were evaluated for efficacy assessments. The mean daily dose of venlafaxine XR in this period was 224.7 mg (SD=66.7). The cumulative probability of recurrence through 12 months, based on the primary definition, was 23.1% (95% CI: 15.3, 30.9) for venlafaxine XR and 42.0% (95% CI: 31.8, 52.2) for placebo (cumulative recurrence comparison P=0.005, log rank test). At month 12, using last-observation-carried-forward analysis, the rate of response or remission was significantly higher in patients who continued treatment with venlafaxine XR (80%) than in those with placebo (69%; P=0.012). Overall discontinuation rates were 49% for venlafaxine XR and 73% for placebo. Rates of discontinuation due to adverse event were 4% for venlafaxine XR and 8% for placebo, and due to unsatisfactory response were 17% for venlafaxine XR and 27% for placebo.

Conclusions: Twelve months of venlafaxine XR maintenance treatment was effective in preventing recurrence in depressed patients who had been successfully treated with venlafaxine XR during acute and continuation therapy.

Session I - 65

Validation of a New Rating Scale for Adherence to Evidence-Based Pharmacotherapy Practices

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Background: The rapid growth of new pharmacotherapies for mood disorders, coupled with the promulgation of numerous practice guidelines, has prompted the need for more systematic approaches to choosing longitudinal treatment strategies. In addition, despite recent efforts to expand effectiveness-based research, practitioners still underutilize findings from evidence-based clinical trials and lack adequate guidance when extrapolating from efficacy-based studies to the needs of "real world" mood disorder patients. The present study sought to address services research needs by devising and validating a new scale to rate fidelity to principles and rationales of evidence-based pharmacotherapy in the treatment of patients hospitalized for mood disorders with comorbid alcohol or drug dependence. A scoring guide was developed in tandem with the rating scale that integrates current findings and levels of evidence from clinical trials as well as recommendations from existing practice guidelines.

Methods: A new 20-item, 20-point rating scale was developed, based on consensus meetings and reviews by key opinion leaders, to identify basic concepts and core principles of evidence-based pharmacotherapy principles and practices for treating mood disorder patients. To increase generalizability for use in routine practice settings, scale items focused on common issues encountered among unipolar or bipolar patients with comorbid substance use disorders. The scale was alpha-tested to rate adherence to evidence-based pharmacotherapy principles among 40 psychiatrists who each had referred an inpatient with DSM-IV unipolar or bipolar mood disorder and comorbid substance dependence. Face validity, internal consistency, and item-total, as well as overall inter-reliability were established. Clinical parameters that could mediate inter-rater reliability were further examined by multiple regression models.

Results: From an original total of 26 scale items, 20 were retained based on item-total Pearson correlations >.80. Internal consistency of the final 20-item scale, as measured by Crohnbach's alpha, exceeded .90. High inter-rater reliability was demonstrated across raters (kappa coefficients >.80). The scale showed robust reliability while controlling for patients' demographic features, clinical severity, illness chronicity, or number of prescribed psychotropic agents.

Conclusions: Prescriber adherence to key principles of evidence-based pharmacotherapy practices can be reliably estimated using a validated rating scale. Longitudinal implementation of the scale may hold value in tracking performance improvement among clinicians or in examining relationships between evidence-based practices and patient service utilization or outcome.

Session I - 66

The Combination of Aripiprazole and Escitalopram in the Treatment of Psychotic Major Depressive Disorder: Efficacy and Tolerability

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Background: Although atypical antipsychotic agents are commonly used in the treatment of psychotic depression, there are few published prospective studies on their use in this condition. The aim of this study was to assess, by interim analyses, the efficacy of the atypical antipsychotic agent aripiprazole in combination with the escitalopram.

Methods: We enrolled 21 patients [10 women (47.6%) and 11 men (52.4%)] with major depressive disorder with psychotic features into an open trial of aripiprazole 5-30mg/day plus escitalopram 10-20mg/day. Patients were assessed at each visit with the HAM-D-17 and both the psychotic and mood modules of the SCID I/P. Responses were defined as: 1) absence of psychotic symptoms with 50% or greater reduction in HAM-D-17 scores (Psychotic Depression Response) and 2) the absence of psychotic symptoms as determined by the SCID psychosis module and a depression rating on the HAM-D-17 of less than 8 (Psychotic Depression Remission). We are reporting the results of the first eight weeks of treatment.

Results: Of the 21 enrolled patients, 11 of these patients [4 women (36.4%) and 7 men (63.6%); mean age: 41.7 + 14.5] completed the 8-week open trial. Of the completers, 78.6% met criteria for melancholic features; 85.7% had delusions alone; 0.0% had hallucinations alone; and 100% reported both delusions and hallucinations. In addition, the completers showed a Psychotic Depression Response rate of 72.7% and a Psychotic Depression Remission rate of 63.6%. Out of the 21 patients enrolled, 10 (47%) patients dropped out prior to completion; 2 (20%) of these drop-outs were due to intolerable side effects. In addition, the authors will review the side effect profile, metabolic changes, and any serious adverse events.

Conclusions: The combination of aripiprazole plus escitalopram appears to be a promising, safe, and effective treatment for psychotic depression. Double-blind studies are needed to confirm this impression.

Poster # I - 67 was not presented at the meeting.

Session I - 68

Weight Effects Associated with Ziprasidone Treatment: A Comprehensive Database Review

Bruce Parsons, M.D., Ph.D. [1], Stephen Murray, M.D., Ph.D. [1], Kathryn Williams, Ph.D. [2], Earl Giller, M.D., Ph.D. [2], Cynthia Siu, Ph.D. [3]

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Background: Weight gain and obesity are linked to an increased risk for cardiovascular disease, diabetes, and hypertension, and some antipsychotics produce weight gain.[1] We examined ziprasidone's clinical trial database to characterize weight change and to explore the relationship between weight change and dose, gender, and duration of ziprasidone treatment.

Methods: Post-hoc integrated analyses of 21 placebo-controlled studies were performed, consisting of 3946 subjects. Patients were classified into three groups: weight unchanged (within 7% of baseline), increased, or decreased (>7% of baseline).

Results: In short-term studies, the majority of patients (80.8-88%) in each ziprasidone dose category were unchanged. There were few differences between the proportions of patients who lost (0.8-4.5%) and those who gained (11.2-14.7%) weight. In long-term studies, the weight change distribution was similar between the combined ziprasidone dose and placebo groups, with the majority of those with weight changes having lost weight. At 6 and 12 months, 50-63.4% of patients remained unchanged, 23.6-41.2% had >7% weight loss, and only 3.7-16.4% had > 7% weight gain. Overall, there was no relationship between the distribution of weight change and ziprasidone dose, treatment duration, or gender.

Conclusions: This comprehensive analysis confirms that ziprasidone is associated with an overall weight neutral profile,[2] with some evidence for weight loss in long-term treatment.

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Session I - 69

Prediction of Combined Symptomatic and Functional Outcome in Patients with Schizophrenia or Schizoaffective Disorder

Ilya Lipkovich, Ph.D. [1], Walter Deberdt, M.D. [2], Peter Buckley, M.D. [3], John Csernansky, M.D. [4], Jozef Peuskens, M.D. [5], Sara Kollack-Walker, Ph.D. [1], John P. Houston, M.D. [1], Ronald Landbloom, M.D. [1], Matt Rotelli, Ph.D. [1]

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Background: An earlier analysis of data from six randomized, active-control studies involving 1449 patients identified five distinct clusters characterized by different combinations of psychiatric and functional outcomes. We explored baseline demographics, disease characteristics, early symptom response, treatment, and adverse events as possible predictors of clusters representing best and worst clinical outcomes.

Methods: At 6-month endpoint in combined treatment groups, good outcome (Cluster A) was associated with good functioning and limited psychopathology. Poor outcome was associated with poor functioning and moderate (Cluster D) or severe (Cluster E) psychopathology. Stepwise logistic regression was used to construct predictive models of cluster membership (N=1260) for baseline predictors and with 2/4/8 weeks of treatment. Odds ratios were adjusted for study effects.

Results: Cluster A baseline predictors included female gender and higher levels of occupational and psychosocial functioning. Greater improvement across PANSS factors during early treatment also predicted good outcome. Cluster D baseline predictors included earlier onset of illness, older age, pseudoparkinsonism, and worse occupational and psychosocial functioning; subsequent worsening in PANSS depression and positive factor scores and in functioning predicted poor outcome for Cluster D. Predictors of Cluster E included earlier onset of illness, non-olanzapine treatment, and higher scores on the PANSS depression, hostility, and positive factors; subsequent worsening in PANSS disorganization, negative, and positive factor scores was predictive of poor outcome for Cluster E.

Conclusions: Early symptom improvement/worsening was predictive of outcome. Early monitoring of psychiatric symptoms and functioning may lead to better therapeutic decisions based on individual characteristics.

Session I - 70

Symptom Worsening Associated with Treatment Discontinuation in Schizophrenia Trials

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Introduction: Treatment discontinuation, common in antipsychotic trials for the treatment of schizophrenia, may be associated with symptom worsening.

Methods: Data from four randomized, double-blind studies (n=1627; 24-28 weeks duration) were used in this pooled post-hoc analysis. Patients with schizophrenia or a related disorder were treated with olanzapine (n=822), risperidone (n=167), quetiapine (n=175), or ziprasidone (n=463). Changes in PANSS total scores (PTS) were analyzed by ANOVA, while generalized estimating equations were used to model discontinuation status versus concurrent PTS changes.

Results: A total of 865 (53%) patients discontinued treatment over the entire study. Mean PTS decreased from 91 to 71 during the study (LOCF; completers from 91 to 59; discontinuers from 91 to 85). Early in treatment (weeks 0-4), discontinuers had no significant change in mean PTS from their previous visit, and 21% of discontinuers (versus 61% of completers) achieved clinical response, defined as 20% or more PTS reduction from baseline. Overall, discontinuers had symptom worsening or less improvement on PTS in the last visit interval. Similarly, individuals who discontinued due to adverse events experienced symptom worsening, or insignificant decreases in PTS compared to their previous visit. Overall, there was a 70% estimated increase in odds for discontinuation for every 10-point PTS increase, within any given visit interval.

Conclusions: Findings from post-hoc analyses of a large pooled sample of patients suggest that failure to establish early treatment response as well as loss of previous symptom improvement may be associated with treatment interruption and discontinuation.

Session I - 71

Evaluating Antipsychotic Dose Response from Flexible-Dose Trials

Ilya Lipkovich, Ph.D. [1], David H. Adams, Ph.D. [1], Craig M. Mallinckrodt, Ph.D. [1], Douglas Faries, Ph.D. [1], David Baron, D.O. [2]

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Background: Assessing dose response for medications tested in flexible-dose clinical trials is problematic. The true dose effect may be obscured and even reversed in observed data because dose and outcome are related. Patients most likely to receive the highest dose are typically those responding poorly but tolerating the drug. Therefore, analyses based on modal or last doses may result in "reversed dose response," where lower efficacy appears associated with higher dose.

Methods: Data from two randomized, double-blind, flexible-dose clinical trials were used. Study A was a 12-week study in acutely ill bipolar I patients with an index manic episode (N=452) who received olanzapine (5, 10, 15, 20 mg/day) or haloperidol (3, 5, 10, 15 mg/day). Study B was a 28-week study in acutely ill patients with schizophrenia or a related disorder (N=339) who received olanzapine (10, 15, 20 mg/day) or risperidone (4, 6, 8, 10, 12 mg/day). To evaluate possible dose effect in primary efficacy scales (YMRS total for Study A and PANSS total for Study B), we used marginal structural models, inverse probability of treatment weighting (MSM, IPTW) methodology. Mean changes from baseline to endpoint were compared between dose groups using weighted ANCOVA models that included terms for modal dose during the last evaluation interval and baseline severity. To adjust for selection bias due to dose assignment and dropouts, patient-specific weights were determined as products of (i) stable weights based on (inverse) probability of receiving the sequence of dose assignments that was actually received by a patient up to the study endpoint, multiplied by (ii) inverse probability of patient remaining on treatment by the study endpoint. The weights were estimated from the data using logistic regression. The results were compared with those by unweighted analysis.

Results: While the observed difference in efficacy scores for dose groups for the unweighted analysis strongly favored lower doses, the weighted analyses showed either no dose effects or superiority of the high dose. This method also removed the bias and recovered the true dose effect in limited situations.

Conclusions: While naïve comparison of groups by last or modal dose in a flexibly dosed trial may result in severely biased efficacy analyses, the MSM approach is a valuable yet underutilized method of (partially) removing these biases and evaluating potential dose effect. The method may prove useful for planning subsequent confirmatory trials.

Session I - 72

Relationship of Family Involvement and Management of Medication Non-Adherence in Schizophrenia

Joshua Wilk, Ph.D. [1], Joyce West, Ph.D., M.P.P. [1], Steve Marcus, Ph.D. [1], Lisa Countis, B.A. [1], Darrel Regier, M.D., M.P.H. [1], Mark Olfson, M.D., M.P.H. [2]

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Objectives: Compare and contrast: specific types of interventions to address medication non-adherence among patients with schizophrenia with high (daily contact with family or live with spouse or parents) versus low levels of family contact; and perceived effectiveness of medication non-adherence interventions among patients with schizophrenia with high versus low levels of family contact.

Methods: A national survey was conducted among a random sample of psychiatrists treating schizophrenia. Each psychiatrist reported on one adult outpatient with schizophrenia who was non-adherent with oral medications at some point in the last year. Sixty-nine percent of eligible psychiatrists responded, resulting in a sample of 295 patients. Patients with high versus low levels of family contact were compared.

Results: Psychiatrists used a family intervention with 67% of the sample. Psychiatrists were more likely to use family interventions to manage medication non-adherence among patients with high family contact, such as teaching the family about the patient's illness and treatment ($p<.01$) and exploring the family's attitudes toward medication ($p<.01$). Although depot medications were reported to be among the most effective interventions for both groups, they were less likely to be used with the high family contact group ($p=.05$). There were generally few differences between patient groups in psychiatrists' perceived effectiveness of psychopharmacological, psychological, and behavioral interventions; however, observed differences were in the direction of greater effectiveness in patients with high family contact. Family interventions generally were rated significantly more effective with patients with high family contact ($p<.01$).

Conclusions: Although previous research suggests family interventions are used with a minority of families, these findings found that psychiatrists reported using family interventions with most patients. Several interventions were reported significantly more effective in the high family contact group, reinforcing the potential benefit of family support in managing antipsychotic non-adherence.

Session I - 73

Psychopharmacology and "The Music Man": "Trouble in the River City" Residency Program

Ira Glick, M.D. [1], Mark H. Rapaport, M.D. [2], Terence A. Ketter, M.D. [1], Sidney Zisook, M.D. [3]

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Background: Despite decades of relative lack of concern, the recent explosion of neuroscience and of outcome research on new drug treatments for psychiatric disorders, in combination with the pressure of psychopharmacology and psychotherapy competency requirements and coupled with changes in ABPN procedures, have created a crisis in the teaching of psychopharmacology to psychiatric residents in many small and mid-size programs.

Methods: A large group of expert psychopharmacologist-teachers from the American Society of Clinical Psychopharmacology (ASCP), with support from a small group of training directors from AAPRT, have combined to produce a fourth edition of the ASCP model psychopharmacology curriculum suitable not only for residency, but also other programs like medical students, industry trainees, etc. to guide the revision. Follow up data was obtained from a survey of users of the first and third editions.

Results: A revised, updated fourth edition has been produced containing: the "why, what, and how" to set up a program, including material on recommended texts and journals, rating scales, use of the internet, and evaluation forms for "course, trainee, teacher and programs," as well as crash-course algorithms. Over 70 lectures (with teaching points and pre-post questions) have been created on PowerPoint covering 1) a crash course, 2) PG II- basic and 3) III-advanced course plus separate lectures for 4) child/adolescent as well as 5) geriatric psychopharmacology. Supplementary lectures on ethics, industry relationships and combining medication with psychotherapy are new. Over 120 programs have adapted all or parts of the curriculum.

Conclusions: Training programs nationally and internationally are obtaining materials (instruments) to have a complete "orchestra" to cope with the challenges of improving psychopharmacology training and competency in practice. For the future, ASCP and AAPRT are partnering for a fifth edition with additional neuroscience and improved pedagogic techniques.

Source of Funding: None

Poster # I - 74 was not presented at the meeting.

Session I - 75

Paliperidone Extended-Release Tablets in the Treatment of Acute Schizophrenia

Stephen Marder, M.D. [1], Michelle Kramer, M.D. [2], Lisa Ford, M.D. [2], Els Eerdekens, M.Sc. [3], Pilar Lim, Ph.D. [2], Marielle Eerdekens, M.D. [3]

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Background: Efficacy, safety, and effect on personal and social functioning and quality of sleep of investigational paliperidone extended-release (paliperidone ER) tablets were assessed in patients with acute schizophrenia.

Methods: This U.S.-based, double-blind, parallel-group, placebo-controlled, 6-week study randomized patients (n=444, age ≥18 years, PANSS total score 70-120) to receive paliperidone ER 6mg or 12mg, placebo or olanzapine 10mg daily. The study was powered to assess efficacy of paliperidone ER vs. placebo. Olanzapine was included for assay sensitivity only.

Results: The ITT set (n=432) was 55% African-American with mean age=41.6±10.7. Significant improvements in the primary efficacy measure (change in PANSS total score at endpoint) were observed for paliperidone ER 6mg and 12 mg (p≤0.006). Scores on the positive, negative, and uncontrolled hostility/excitement Marder PANSS factor scales also improved significantly (p<0.025). Personal and Social Performance scale assessed patient function and scores for the paliperidone 6mg group significantly improved at endpoint vs. placebo (6mg=8.8±13.9 [p=0.008], 12mg=6.6±13.1 [p=0.214], placebo=2.9±13.0). Mean change at endpoint for quality of sleep, as assessed by a patient-rated Visual Analog Scale (VAS), was significantly improved for paliperidone ER vs. placebo: 6mg=+8.3±33.4 (p=0.009), 12mg=+6.8±35.0 (p=0.016), placebo=-3.3±36.2. There was no statistically significant difference in change at endpoint in daytime drowsiness VAS score for paliperidone ER vs. placebo. TEAE occurring >3% more frequently than with placebo were headache and dry mouth (paliperidone ER), and somnolence, anorexia, and increased serum glutamic oxaloacetic transaminase (olanzapine). EPS-related AEs were comparable in the paliperidone ER 6mg, olanzapine, and placebo groups, but higher with paliperidone ER 12mg. SAE frequency was 8% with paliperidone ER, 11% with olanzapine, and 10% with placebo.

Conclusions: This study showed that treatment with paliperidone ER 6mg and 12mg significantly improved symptoms of acute schizophrenia and was well tolerated in these patients. Patients also experienced improvements in personal and social functioning and quality of sleep.

Session I - 76

The Association of Depression with Psychopathology, Cognition, and Functional Status in Chronic Schizophrenia

Cecile Sison, Ph.D. [1], Edward Allan, M.D. [1], Kushik Jaga, M.B.B.S., M.P.H. [1], Christopher R. Bowie, Ph.D. [2], Philip D. Harvey, Ph.D. [2]

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Objective: Depression is a common comorbid condition in schizophrenia. The objective of this study is to examine the relationship between depression, psychopathology, cognition, and functional status in chronic schizophrenia, and to consider implications for improving cognitive and functional status with appropriate treatment of depression.

Methods: Forty-six VA patients living independently and in community care participated. All participants had a confirmed diagnosis of either chronic schizophrenia or schizoaffective disorder and a mini-mental score (MMSE) above 18. Depression was assessed with the Beck Depression Inventory (BDI) and psychopathology was rated with the Positive and Negative Symptoms Scale (PANSS). Cognitive status was assessed with neuropsychological tests and functional status with the UCSD Performance-based skills Assessment (UPSA) and Specific Level of Functioning (SLOF). Comparisons were made between a depressed group of patients with a BDI score of 10 and above versus a non-depressed group.

Results: All patients were males with a mean age of 59 years, mean educational level of 12.6 years, and a mean MMSE of 26.2. The depressed group had significantly higher psychopathology ($p<0.01$) in the PANSS general psychopathology subscale. There was a trend in lower physical functioning, but no other differences in cognitive and functional status between the two groups. Correlations between BDI scores and the other measures showed a significant correlation with decreased physical functioning, interpersonal relationships, and social acceptability, but not with PANSS negative and positive symptoms. In a subgroup of 15 patients followed up after 18 months, there was a trend toward higher BDI scores ($p=0.092$) and functional status decrease in the Total SLOF scores ($p=0.036$). In contrast, the total PANSS scores showed significant improvement after 18 months ($p=0.001$), including significant improvement in the PANSS positive symptoms and psychopathology subscales.

Conclusions: Our findings suggest a relationship between depression and general psychopathology in chronic schizophrenia. Depression could be differentiated from negative symptoms through somatic, physical changes in functioning as well as differences in outcome. The somatic equivalent of depression is physical functioning status as reflected by the SLOF physical functioning scale. Assessment of functional capacity is an important component in the care of depressed schizophrenic patients. Different courses of affective and positive and negative symptoms of schizophrenia, as well as divergence in correlations with functional measures, suggest that these are distinct symptom dimensions in schizophrenia.

Session I - 77

Use of Long-Acting Antipsychotic Injection Medications for Medication Non-Adherence in Schizophrenia

Joyce West, Ph.D., M.P.P. [1], Joshua Wilk, Ph.D. [1], Steve Marcus, Ph.D. [1], Lisa Countis, B.A. [1], Darrel Regier, M.D., M.P.H. [1], Mark Olfson, M.D., M.P.H. [2]

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Objective: Describe patient and psychiatrist characteristics associated with initiation of long-acting antipsychotic injections in a nationally representative sample of psychiatric outpatients with schizophrenia and recent medication non-adherence.

Methods: A national survey was conducted among a random sample of psychiatrists treating schizophrenia. Each psychiatrist reported on one adult outpatient with schizophrenia who was non-adherent with oral medications at some point in the last year. Sixty-nine percent of eligible psychiatrists responded, resulting in a sample of 295 patients. Rates of initiating long-acting injections are compared across patient and psychiatrist characteristics.

Results: Of patients studied, 17.6% initiated long-acting antipsychotic injections. In regressions controlling for relevant patient and psychiatrist characteristics, initiating long-acting injections was significantly and positively associated with public health insurance (OR=19.0; 95% CI 2.3-160.4); inpatient admission during the episode of non-adherence (OR=3.3; 95% CI 1.6-7.1); medication non-adherence for a greater proportion of time under treatment (OR=2.6; 95% CI 1.1-5.9); average or above average intellectual functioning (OR=2.8; 95% CI 1.1-7.4); and living in a mental health residence (OR=4.1; 95% CI 1.4-12.3). Use was inversely associated with using second-generation antipsychotics (OR=.23; 95% CI .1-.6) and other oral psychotropic medications prior to medication non-adherence (OR=.3; 95% CI=.1-.8). Psychiatrists who were male (OR=3.0; 95% CI 1.2-7.7), nonwhite (OR=2.1 (95% CI 1.1-4.3), and more optimistic about management of non-adherence (OR=6.1; 95% CI 2.3-16.6) were more likely to initiate long-acting injections.

Conclusions: Despite clinical recommendations urging use of long-acting preparations for schizophrenia patients with medication non-adherence, they are uncommonly used in practice. Initiation of long-acting antipsychotic injections appears to be a joint function of patient, physician, treatment, and setting-related factors.

Session I - 78

A 12-Week Open-Label Study of High-Dose Quetiapine in Treatment-Resistant Schizophrenia

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Background: Clozapine has been proven to be the most effective treatment for patients with treatment-resistant schizophrenia. However, constant monitoring and potential for serious side effects has limited its use in clinical practice. Few controlled studies have evaluated the efficacy of quetiapine in treatment-resistant schizophrenia when dosed above 800 mg/day.

Methods: Schizophrenia subjects, with at least two previous periods of adequate antipsychotic treatment without clinically significant symptom improvement, were enrolled in an open-label trial of quetiapine with a target dose of 1200 mg/day (range 1000 – 1400 mg/day).

Results: Twelve subjects were enrolled in the study. Four subjects completed the 12-week evaluation. Two subjects withdrew due to administrative issues; none of the patients discontinued the study due to safety concerns about the medication. The mean total BPRS score entering the study was 53.9(SD = 10.8) and mean CGI score was 4.9(SD = 0.7). A non-significant decrease in BPRS total score and CGI score occurred during the study, -3.7(SD = 10.9) and -0.1(SD = 0.7), respectively. However, the BPRS subscale for positive symptoms trended towards significance -2.1(SD = 3.6) (t = -1.97, df = 11, p = 0.0739). Two patients (17%) responded to treatment, defined as a 20% reduction in BPRS score. The most frequent reported side effect was somnolence/lethargy (n = 5).

Conclusions: High-dose quetiapine was safe, but not robustly effective for patients with treatment refractory schizophrenia. Larger studies are needed to confirm these findings.

Session I - 79

Study Design and Study Burden May Impact Treatment Discontinuation Rates

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Objectives: To assess whether study design and the burden placed on study participants impacts treatment discontinuation rates in studies of antipsychotics for the treatment of schizophrenia.

Methods: We searched for publications and presentations of antipsychotic studies in the treatment of schizophrenia that were at least 1-year long, relatively recent (1997-2004), conducted in or predominately in the United States, had more than two treatment arms, and differed in methodology to reflect (a) randomized double blind design, (b) randomized double blind permitting antipsychotic switching, (c) randomized open label permitting antipsychotic switching, and (d) non-randomized non-interventional naturalistic design. Rates of treatment discontinuation for any cause were examined by study design and by level of burden on study participants, as assessed by the number of scheduled study visits, number of assessments per visit, and estimated duration of assessments. Discontinuation rates were also assessed for specific antipsychotic medications by study design and by study burden.

Results: Four studies met inclusion criteria, reflecting randomized double blind design (Lilly-sponsored, HGGN); randomized double blind permitting antipsychotic switching (NIMH-sponsored CATIE); randomized open label permitting antipsychotic switching (Lilly-sponsored, HGGD); and non-randomized non-interventional naturalistic study (Lilly sponsored, US-SCAP). High study burden and randomized double blind study design were associated with the highest 1-year overall treatment discontinuation rate (66%). Lower overall treatment discontinuation rate was found in the randomized open label permitting antipsychotic switching (58%), and lowest overall treatment discontinuation rate was observed in the non-randomized non-interventional naturalistic design (50%), which also had the lowest study burden. The same pattern was found for each antipsychotic treatment group (olanzapine, risperidone, and typical antipsychotics). In addition to study design and burden on study participants, rates of treatment discontinuation for any cause differed by antipsychotic medication, and were consistently lowest for the olanzapine treatment group.

Conclusions: Treatment discontinuation rates may be found to be optimistically low or pessimistically high depending on study design, burden level on study participants, and treatment with specific antipsychotic medications. Findings suggest that study design and burden on study participants appear to be among several factors that influence rates of treatment discontinuation for any cause in the treatment of schizophrenia.

Session I - 80

Determining the Mechanism of a Drug-Drug Interaction: Venlafaxine and P-Glycoprotein

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Objectives: The objective of this study was to evaluate the effect of treatment with venlafaxine on the expression of P-glycoprotein(Pgp) and multidrug resistance-related proteins (MDR) in colon carcinoma cells (Caco-2) in comparison to a known Pgp inducer, rifampin.

Methods: Caco-2 cells were treated with venlafaxine (50μM, 100μM, 250μM, and 500μM) to test for the possible induction of Pgp and MDR expression in comparison to rifampin (25μM and 50μM). Several different concentrations of the medications were studied, because relatively few studies have been done in this area. The treatment times used were 1.5, 3, 6, 12, 24, 48, and 72 hours. RNA was isolated from the cells, and MDR and Pgp genes were amplified using PCR. Ethidum bromide electrophoresis gels were run to verify the PCR products, and quantification of amplification was determined using ImageJ software available from the National Institutes of Health.

Results: Both venlafaxine and rifampin had the most dramatic effect at the 50μM concentration. There was an increase in MDR and Pgp expression in Caco-2 cells after the acute treatment (1.5, 3, and 6 hours) with venlafaxine. After 12 hours, a decrease was seen in the expression of MDR and Pgp. This decrease could be attributed to cell death, due to overgrowth in the flask or lack of essential nutrients due to unchanged growth medium. There was a similar response with the known inducer, rifampin.

Conclusions: Pgp contributes to renal and biliary elimination of drugs by transporting the drug out of the cell and back into the intestinal lumen, where drugs may be further metabolized by intestinal enzymes such as Cytochrome P (CYP)-450 3A4. This would limit the bioavailability of the compound. Due to the increase in MDR and Pgp expression seen after the acute treatment with venlafaxine, there could be a potential drug-drug interaction with medications that are metabolized via CYP450-3A4 with coadministration of venlafaxine (such as protease inhibitors). This has been demonstrated clinically in a previous normal volunteer study.[1]

Future studies in this area could include investigating other cell lines to determine if the same ratio of increase in MDR and Pgp exists, and if the only active metabolite of venlafaxine, o-desmethylvenlafaxine, has a role in a further potential increase in MDR and Pgp expression.

References:
[1]Levin GM, Nelson LA, DeVane CL, Preston SL, Eisele G, Carson SW. A pharmacokinetic drug-drug interaction study of venlafaxine and indinavir. Psych Bull 2001;35:62-71.

Session I - 81

Early Response to Antipsychotics as Predictor of Later Response in the Naturalistic Treatment of Schizophrenia

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Objective: To assess whether early response to antipsychotic medication (at 2 weeks) accurately predicts later response (at 8 weeks) in the naturalistic treatment of schizophrenia.

Methods: Data were drawn from a randomized, open-label trial (N=664) of olanzapine, risperidone, and typical antipsychotics in the treatment of schizophrenia, completed in September 2002. Treatment response was defined as at least 20% improvement on the PANSS total score from baseline ("minimal improvement"). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall predictive accuracy were calculated for response/non-response at 2 weeks and subsequent response/non-response at 8 weeks. Analyses were repeated using mild or better scores on four PANSS psychotic items to define response.

Results: Early response/non-response predicted subsequent response/non-response with high overall accuracy (72.8%), moderate PPV (69.4%), high NPV (73.8%), moderate sensitivity (42.4%), and high specificity (89.7%). Results were similar when four PANSS psychotic items defined response/non-response.

Conclusions: In the naturalistic treatment of schizophrenia, early response/non-response to treatment with antipsychotics appears to accurately predict subsequent response/non-response to treatment. Findings suggest that early non-responders may benefit from change in antipsychotic regimens to avoid prolonging exposure to sub-optimal treatment alternatives. Findings are consistent with previous research on early prediction of antipsychotic response in schizophrenia.

Session I - 82

The 3-Year Course of Schizophrenia Among Persons with Tardive Dyskinesia and Persons Without

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Objective: To compare the 3-year course of schizophrenia between persons with tardive dyskinesia (TD) and persons without.

Methods: Data were drawn from a large, prospective, naturalistic study of persons treated for schizophrenia in the United States, conducted between July 1997 and September 2003. Treatment outcomes were assessed at 12-month intervals using standard psychiatric measures and medical record abstraction. Using repeated measures analyses, participants with probable TD at enrollment (fulfilling Schooler-Kane criteria, N=621, 29.5%) were compared with participants who did not (N=1482), on clinical and functional measures across the 3-year study.

Results: Across the 3-year study participants with TD had significantly more severe psychopathology (PANSS total score, negative symptoms, positive symptoms, general psychopathology), were less likely to experience symptom remission, had more severe EPS and had poorer level of functioning (e.g., productivity level, employment, daily activity, GAF, Quality of Life Scale and its four domains). Results were essentially unchanged following adjustments for known correlates of TD and when using a subgroup of participants with persistent TD (at enrollment and at 1 year).

Conclusions: In the long-term treatment of schizophrenia, persons with TD have a significantly more severe and more refractory course of illness than persons without TD, suggesting poorer prognosis and need for specialized interventions.

Session I - 83

Effects of Aripiprazole on Reproductive Endocrine Parameters

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Background: Antipsychotic drug-induced hyperprolactinemia may cause distressing side effects, such as sexual dysfunction. The objective of the study was to analyze the effects of aripiprazole on prolactin levels and reproductive-related adverse events from controlled clinical trials.

Methods: We analyzed rates of hyperprolactinemia, defined by prolactin levels greater than the upper limit for normal (ULN) and within normal limits at baseline, in 35 clinical studies. Rates of the COSTART-defined adverse effects in aripiprazole patients, placebo groups, and comparator groups were analyzed descriptively: decreased libido, impotence, and gynecomastia for men, and dysmenorrhea and galactorrhea for women. Fisher's exact test was used for statistical comparisons.

Results: A total of 6699 patients were analyzed, 1170 in bipolar I disorder and 5529 in schizophrenia. Overall, hyperprolactinemia occurred in 110/2540 (4.3%) aripiprazole patients. In comparator-drug studies of schizophrenia, significantly less hyperprolactinemia occurred in aripiprazole-treated patients (11/609; 1.8% $p < .01$) versus placebo (20/286; 7.0%), while hyperprolactinemia was significantly higher than placebo ($p < .01$) for both haloperidol-treated (80/148; 54%) and risperidone-treated patients (75/84; 89%). The rate of each AE (decreased libido, impotence, or gynecomastia) was < 1% in men (N = 3975). In women, (N = 2724) the rate of decreased libido and of galactorrhea was < 1%. The overall rate of dysmenorrhea was 2.5% for aripiprazole (69/2724), and the placebo rate in short-term trials was 3.7% (13/347). Placebo and comparator drug rates of reproductive AEs were comparable to aripiprazole, with one exception: in a trial of bipolar disorder, 8/169 haloperidol patients had decreased libido versus 0/175 aripiprazole patients, with hyperprolactinemia rates of 40/84 (47.6%) for haloperidol and 9/101 (8.9%) for aripiprazole.

Conclusions: The low rates of hyperprolactinemia and spontaneously-reported AEs related to reproductive function in aripiprazole-treated patients, notably the <1% rate of decreased libido, suggest aripiprazole will have minimal adverse effects on sexual function. Sexual dysfunction and reproductive side effects were among the leading adverse events identified by systematic inquiry in the CATIE trial;[1] thus further comparative studies of the effects of atypical antipsychotic agents on sexual function are warranted.

Reference:
[1]Lieberman et al., N Engl J Med. 2005 Sep 22;353(12):1209-23.

Session I - 84

Clinical Remission and Cognitive Improvement in Schizophrenia: Lack of Correlation Between Domains of Improvement

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Background: A systematic definition of remission in schizophrenia has been recently proposed which describes clinical changes associated with an essentially clinical symptom-free state. However, it is also known that cognitive impairments are possibly better predictors of functional outcomes than clinical symptoms. Understanding the relationship between clinical remission and cognitive improvement may be required in order to best predict functional improvements. We examined the development and prevalence of sustained clinical remission and the association of neuropsychological improvements with remission in a large sample of patients with schizophrenia whose medication was switched to ziprasidone.

Methods: One hundred eighty-four patients were switched from their previous treatment with risperidone, olanzapine, or conventional antipsychotics to open-label ziprasidone treatment. One hundred thirty-seven patients were not in remission at baseline, and 40 met the clinical criteria for remission at study entry. We rated their symptoms with the PANSS at baseline prior to the switch and after 6 weeks and 6 months of treatment. We also performed a neuropsychological assessment, which was used to generate a composite score which was examined for improvements in the same time frame.

Results: Of the 184 cases, 48 (26.1%) met the remission criteria at baseline. Of these cases, 41 (85% of the cases who started in remission) sustained their remission at the 6-month follow-up. Of the remaining 136 cases, 60 (33%) developed remission by 6 weeks and sustained it at the 6-month follow-up. Thus, a total of 101 of 184 cases (55%) were in remission at the 6-month endpoint. A comparable number of the patients, 59 (34%), improved by 0.5 SD or more in their cognitive performance. There were no baseline differences in cognitive performance between those patients who were and were not in remission, and cognitive performance at baseline did not predict achieving remission. Further, development of clinical remission was not correlated with concurrent cognitive improvements. However, 33 patients both achieved clinical remission and also improved by 0.5 SD in their cognitive performance.

Conclusions: After a switch from previous treatment to open-label ziprasidone, more than half of patients with schizophrenia experienced sustained clinical remission over 6 months, and 32% of patients achieving remission experienced a substantial concurrent cognitive improvement. Thus, there was a reasonable proportion of patients who manifested substantial clinical and cognitive improvements. Since cognitive performance at baseline and cognitive changes did not converge overall with development of clinical remission, later research will be required to determine which aspects of improvement (clinical remission and/or cognitive improvements) are required for functional improvements.

Session I - 85

Development of New Rating Scale for Negative Symptoms

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Background: Based on the identification of specific behavior related to negative symptoms, we aimed to develop a new rating scale for negative symptoms (the Motor-Affective-Social Scale, or MASS) that will show good psychometric properties.

Methods: During a 5-minute structured interview, hand coverbal gestures, spontaneous smiles, voluntary smiling, and questions asked by the interviewer were counted and rated with 85 inpatients (including 31 women) with a SCID diagnosis of schizophrenia or schizoaffective disorder. Information on social behavior (hygiene, participation in groups, and verbal interaction) was obtained from nursing staff. Seven items were selected and were rated from 1 to 4.

Results: Inter-rater reliability was calculated utilizing four raters with 12 patients for the MASS patient interview and with 24 patients for the unit social behavior questions. Intraclass correlation coefficients for each item were all above 0.90. Internal consistency (raw and standardized Cronbach alpha coefficients) reached 0.81. Test-retest reliability was evaluated with the use of a mixed model analysis: intraclass correlations were 0.84 for total scores, 0.73 for interview scores, and 0.74 for unit behavior questions. Convergent validity was evaluated by correlations between MASS total scores (range: 7-28, a higher score meaning less negative symptomatology) and clinical ratings. With the small-angle neutron scattering, correlation reached –0.82; with the PANSS Negative Symptom Subcale, correlation was –0.80 when rating was done during interview, and –0.77 when rating was done by a blind rater, and with the Occupational Therapy Task Observation, correlations were 0.40 with the Task Behavior subscale and 0.57 with the General Behavior subscale. Discriminant validity was assessed with the MADRS and the PANSS Positive Symptom subscale; MASS scores did not correlate significantly with these two measures (r= -0.06 and 0.17 respectively).

Conclusions: The MASS is based on the findings that negative symptoms can be grouped into two categories: expressiveness during an interview, and certain social behavior. For the interview, specific behaviors are defined and their occurrences are counted, thus avoiding subjective impressions and the influence of global impression on item ratings. The MASS can be easily learned, is easily administered, and is brief (five minutes). Future research will include the use of the MASS with other patient populations (outpatients, patients with depression), as well as the sensitivity of the scale during clinical trials.

References:
Trémeau F, Malaspina D, et al. Facial expressiveness in patients with schizophrenia compared to depressed patients and nonpatient comparison subjects. Am J Psychiatry. 2005 Jan;162(1):92-101.

Session I - 86

Comparison of Olanzapine, Quetiapine, and Risperidone in First-Episode Psychosis: A Randomized, 52-Week Trial

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Objective: To evaluate the overall effectiveness of olanzapine, quetiapine, and risperidone in patients experiencing a first psychotic episode.

Methods: A 52-week, randomized, double-blind, multicenter study of first-episode patients with a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients were randomized to olanzapine (2.5 to 20 mg/d), quetiapine (100 to 800 mg/d), or risperidone (0.5 to 4 mg/d). Clinicians were encouraged to lower the antipsychotic dose to relieve extrapyramidal symptoms (EPS). The primary outcome measure was the rate of all-cause treatment discontinuation up to 52 weeks. Statistical analysis tested for non-inferiority in all-cause treatment discontinuation rates between quetiapine and olanzapine or risperidone based on a 20% non-inferiority margin.

Results: Four hundred patients were randomized to olanzapine (N=133), quetiapine (N=134), or risperidone (N=133) treatment. The majority of patients had a diagnosis of schizophrenia (57.8%). The mean modal prescribed daily doses for olanzapine, quetiapine, and risperidone were 11.7 mg, 506 mg, and 2.4 mg, respectively. At endpoint, the all-cause treatment discontinuation rates were similar: 68.4%, 70.9%, and 71.4% for olanzapine, quetiapine, and risperidone, respectively. All treatments showed reductions in mean PANSS total, CGI severity, and CDSS total subscale scores at Week 52, with no significant differences between treatments. Common elicited adverse events in all groups were daytime drowsiness and weight gain.

Conclusions: Olanzapine, quetiapine, and risperidone, at mean modal doses of 11.7 mg/d, 506 mg/d, and 2.4 mg/d, respectively, demonstrate similar rates of all-cause treatment discontinuation and produce similar improvements in psychopathology, but differ in their safety and tolerability profiles.

Session I - 87

A Double-Blind, Placebo-Controlled Trial of the Effects of Transdermal Nicotine on Reward Responsivity in Non-Smokers with Schizophrenia

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Background: The high prevalence of smoking in schizophrenia may be due to beneficial effects from nicotine on symptoms of schizophrenia such as anhedonia. Nicotine may ameliorate dysfunctional dopaminergic pathways facilitating the experience of pleasure and satisfaction. The atypical antipsychotic clozapine reduces negative symptoms, anhedonia, tobacco and other substance use and may reduce the euphoriant effects of cocaine in individuals with schizophrenia. We investigated the effects of nicotine when added to clozapine or other antipsychotic medications in non-smokers with schizophrenia, with the hypothesis that nicotine would improve reward responsivity in non-smokers with schizophrenia not treated with clozapine.

Methods: We conducted a randomized, double-blind, placebo-controlled, crossover trial of a 14 mg transdermal nicotine patch, dosed for four hours, on responsivity to reward as measured by a novel signal detection task in non-smokers with schizophrenia. Subjects completed a baseline rating after enrollment and then received each of two treatments, 14 mg transdermal nicotine patch and identical placebo patch in random order one week apart. Tests were performed at the baseline visit and then 4 hours after application of each patch.

Results: Nicotine had a greater effect on reward responsivity in patients with schizophrenia not treated with clozapine (n=9) compared with clozapine treated patients (n=7). In block 2, non-clozapine treated subjects showed a positive mean response bias in the nicotine condition, 0.216 (0.30), while clozapine treated subjects did not, -0.105 (0.28), t=-2.18, p=0.046. In block 3, non-clozapine treated subjects also had greater mean response bias, 0.27 (0.22) versus clozapine subjects, 0.014 (0.20), t= -2.38, p= 0.032. In a two-way ANOVA with medication (clozapine vs. non-clozapine) as the between group factor and patch condition (nicotine vs. placebo) as the within group factor, the overall model was significant ($F_{(1, 95)}$ =2.12, p=0.0269), the main effect of clozapine approached significance (F=3.90, p=0.0514), and the clozapine by nicotine interaction was significant (F=6.11, p=0.0155).

Conclusions: Clozapine modulates the effect of nicotine on reward responsivity in individuals with schizophrenia. Reward responsivity did not improve with nicotine in those on clozapine, while the improvement was robust in those on other antipsychotics. Patients on clozapine may smoke less because they experience fewer pleasurable effects from smoking. These results suggest that nicotine and clozapine may work through complementary pathways such as improving dopaminergic or glutamatergic transmission.

Session I - 88

Remission in Schizophrenia: A Comparison of Two Dose Regimens of Ziprasidone Versus Haloperidol Treatment in a 40-Week Core and 3-Year Double-Blind Extension Study

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Background: The efficacy and tolerability of atypical antipsychotics in comparison with conventional agents has not been well studied in the long-term treatment of schizophrenia.[1] We compared the effectiveness of two dose regimens of ziprasidone (BID 80-160 mg/d; N=72 or QD 80-120 mg/d; N=67) with haloperidol (5-20 mg/d; N=47) in subjects with schizophrenia over a 40-week double-blind core and 3-year (156 weeks) double-blind extension study.

Methods: Efficacy evaluation was based on recently proposed remission criteria for schizophrenia[2] which require maintenance, over a 6-month period, of ratings of mild or less (≤ 3) on 8 PANSS items. The cross-sectional remission (symptom-severity component only) and quality of life measures over time (at weeks 6, 16, 28, 40, 68, 92, 124, 148, 172, and 196) were analyzed using Generalized Estimating Equations (GEEs).

Results: Ziprasidone treatment was associated with higher rates of remission vs. haloperidol (using severity criteria) at all visits during years 2-4. Compared to haloperidol, ziprasidone treatment resulted in a significantly higher proportion of patients meeting full remission criteria ($p < 0.05$) in the final 6 months of the study. Both ziprasidone BID and QD groups showed significantly greater improvement in QLS scores than haloperidol over the 3-year extension phase. These differences were explained in part by improvement in remission status with ziprasidone ($p < 0.001$ mediation coefficient).

Conclusion: In this randomized, double-blind, long-term (40-week core and 3-year extension) study, both BID and QD dose regimens of ziprasidone were associated with continued improvement in remission and quality of life, in contrast to haloperidol.

References:
[1]Lieberman JA, Stroup TS, McEvoy JP et.al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209-1223
[2]Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in Schizophrenia: Proposed criteria and rationale for consensus. Am J Psychiatry 2005;162:441-449.

Session I - 89

Long-Term Symptomatic Remission in Schizophrenia Patients Treated with Aripiprazole or Haloperidol

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Background: Schizophrenia is a debilitating, life-long disease for which full recovery is typically not considered as a realistic treatment endpoint. Symptomatic remission, however, may be an objectively attainable treatment goal. We studied symptomatic remission rates within a 52-week period for patients diagnosed with schizophrenia and treated with either aripiprazole or haloperidol.

Methods: Data were analyzed from a double-blind, comparative trial in which patients (18-65 years) with acute schizophrenia were randomized to either aripiprazole (n = 851) or haloperidol (n = 430) and treated for 52 weeks. Remission status of patients was evaluated based on recently developed remission criteria (i.e., scores =3 on 8 specific Positive and Negative Syndrome Scale [PANSS] items for =6 months). Statistical evaluations included last observation carried forward (LOCF) and observed case (OC) analyses of remission rates, survival analysis of time to achieve remission, and treatment group comparisons of Clinical Global Impression-Improvement (CGI-I) scores, adverse event (AE) related discontinuation rates, and rates of medication use to treat extrapyramidal symptoms (EPS).

Results: Significantly more aripiprazole-treated patients satisfied the criteria for symptomatic remission than those treated with haloperidol (32% vs. 22%; P < 0.001, LOCF). Additionally, aripiprazole-treated patients experienced a significantly shorter time to achieve remission than haloperidol-treated patients (log-rank P = 0.0024). Patients in both groups who completed the trial showed high rates remission (aripiprazole: 77%, haloperidol: 74%, OC), which were not statistically different. In general, patients achieving remission showed significant improvement on the CGI-I at endpoint compared with non-remitters (P < 0.0001, both groups). Significantly fewer aripiprazole-treated patients discontinued the study due to AEs compared with haloperidol-treated patients (8% vs. 18%, respectively, P < 0.001). Furthermore, significantly fewer aripiprazole-treated patients received concomitant EPS medication compared with haloperidol-treated patients (23% vs. 57%, respectively; P < 0.001).

Conclusions: Significantly more aripiprazole-treated patients achieved symptomatic remission in a shorter period of time compared with haloperidol-treated patients. Aripiprazole treatment was also associated with fewer AE-related trial discontinuations and lower concomitant EPS medication use. Coupled with the finding that remission rates did not differ by treatment group for the trial completers, these results suggest that better tolerability may have contributed to the increased remission rates among aripiprazole-treated patients.

Session I - 90

Effects of Hepatic Impairment on the Pharmacokinetics of Immediate-Release Paliperidone

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Background: Paliperidone is an investigational psychotropic for the treatment of schizophrenia. Paliperidone is mainly renally excreted in humans (59%). Although no major metabolic pathways were identified, more than 20% of the absorbed paliperidone is metabolized. An abbreviated study design was selected to assess the impact of hepatic impairment on plasma and urine pharmacokinetics of orally administered, immediate-release (IR) paliperidone.

Methods: This study was a single-dose, parallel-group study in 10 subjects with moderate hepatic impairment (Child-Pugh class B: total score 7-9) and 10 demographically matched subjects with normal hepatic function. One mg IR paliperidone was administered as oral solution. Plasma and urine sample collection for pharmacokinetic analysis was performed predose and regularly after dosing up to 96 hours.

Results: Lower plasma protein binding was observed in hepatically impaired subjects, and consequently a higher unbound fraction (35%) compared to that in healthy subjects (28%) was noted. Mean C_{max} and AUC_{∞} for total paliperidone were lower in subjects with moderate hepatic impairment (4.57 ng/mL and 128 ng.h/mL, respectively) compared to healthy subjects (7.14 ng/mL and 176 ng.h/mL, respectively). After taking into account the reduced protein binding, plasma and urine exposure for the unbound fraction was comparable between both groups (unbound C_{max} 1.81 vs. 1.59 ng/mL, unbound AUC_{∞} 45.8 vs. 45.7 ng.h/mL, non-renal clearance 188 vs. 205 mL/min and Vd_z 748 vs. 857 L for healthy subjects vs. hepatic impaired, respectively). The time to maximal concentration (approximately 1 hour) and the terminal half life (approximately 1 day) was not affected by hepatic function. Adverse events reported in at least two subjects per group were hyperprolactinaemia and dizziness.

Conclusions: Total exposure is somewhat reduced in subjects with moderate hepatic impairment (27%). After taking into account the reduced protein binding, unbound plasma paliperidone concentrations are similar between subjects with moderate hepatic impairment and healthy subjects. As unbound concentrations are believed to be most relevant for efficacy and safety, based on the pharmacokinetic data observed in this study, no dose adjustment is required in patients with hepatic impairment.

Session I - 91

Neuroactive Steroids, Estrogen, and Sertraline in Menopausal Depression

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Objective: Prior literature suggests that neuroactive steroids (NAS) may play an important role in mood disorders; this area remains under-examined in patients with depression, both in comparisons with healthy controls and within subjects over the course of antidepressant treatment. We evaluated NAS profiles in postmenopausal women, with or without major depression, by examining serum levels of allopregnanolone, allotetrahydrodeoxycorticosterone (THDOC), progesterone, and DHEA. We then investigated whether the administration of exogenous estrogen versus placebo influenced NAS concentration longitudinally. Lastly, we compared NAS concentrations in depressed subjects who remitted at the end of a 10 week treatment trial versus nonremitters.

Methods: Twenty-eight postmenopausal women (16 with major depression and 12 healthy controls) were randomized to transdermal estrogen patch or placebo patch in a double blind manner. Patches were applied twice weekly for 10 weeks (estrogen patch release rate of 0.1 mg e2/day). NAS levels were measured at baseline and week 10. Depressed subjects were treated with 50 mg/day of sertraline for the first week of treatment and then increased to 100 mg/day for 9 weeks. The 17-item Hamilton Depression rating Scale (Ham-D) was administered each week, with remission defined as Ham-D = 5 at study end.

Results:
Pretreatment NAS levels in Depressed and Control Subjects: Prior to treatment, total NAS levels were significantly lower in the depressed subjects ($F(4,23) = 4.99$, $p= .005$). Follow-up statistical tests revealed that allopregnanolone and DHEA were the strongest contributors.

Exposure to Estrogen versus Placebo and Change in NAS Levels: Neither estrogen nor placebo had a significant effect on changing NAS concentration at week 10, for depressed or control subjects.

Change in NAS levels in remitters and nonremitters: Of the 16 depressed subjects, 10 were remitters. THDOC decreased in remitters and increased in nonremitters ($p = .003$ for the interaction term); likewise, DHEA decreased in remitters and increased in nonremitters ($p= 0.39$ for the interaction term). There was no difference in remitters and nonremitters on estrogen versus placebo.

Conclusions: Neuroactive steroid profiles differed in postmenopausal women with major depressive disorder and normal controls. Treatment with estrogen was not associated with changes in neuroactive steroids; however, clinical response during treatment with the SSRI sertraline, with or without estrogen, resulted in significant alterations in NAS. Symptoms of depression may be influenced by the synthesis and fluctuation of neuroactive steroids. The clinical importance of NAS in mood disorders across the life span needs further exploration.

Session I - 92

Cognitive Testing in Early-Phase Clinical Trials: Development of a Rapid Computerized Test Battery and Application in Simulated Phase I Study

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Background: Inclusion of cognitive assessment in Phase I trials of novel pharmaceutical agents may help identify subtle yet meaningful CNS effects early in clinical development.

Aims: To examine practical issues surrounding the use of a brief computerized cognitive test battery in Phase I clinical trials. To determine the sensitivity of this test battery to cognitive changes associated with the administration of the sedative-hypnotic midazolam.

Methods: A 12-minute battery of five computerized cognitive tasks was administered to 28 healthy male volunteers enrolled in a double-blind, dose-escalation study using three doses of midazolam (0.6mg, 1.75mg, 5.25mg) with pseudo-randomized placebo insertion. Subjects were enrolled and assessed at two different Phase I units.

Results: All subjects completed all stages of the study. There were no significant differences in data collected between sites. All standard safety measurements were completed. No substantial technical issues were noted. ANOVA comparing baseline to post-baseline results revealed significant cognitive deterioration on all tasks one hour following administration of 5.25mg midazolam. Smaller but significant changes were observed on a subset of memory and learning tasks at 1 hour post-dosing in 1.75mg condition, and at 2 hours post-dosing in the 5.25mg condition.

Conclusions: The cognitive test battery developed for this study was well tolerated by study subjects and Phase I unit staff. The tests demonstrated minimal learning effects, were unaffected by language and cultural differences between sites, and were sensitive to the sedative effects of midazolam. Inclusion of this cognitive test battery in future studies may allow identification of cognitive impairment or enhancement early in clinical development.

Session I - 93

Mifepristone for the Prevention of Olanzapine-Induced Weight Gain in Rats

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Objectives: Using a model of olanzapine-induced weight gain in rats, (a) test whether mifepristone reverses olanzapine-induced weight gain, and (b) test whether mifepristone prevents olanzapine-induced weight gain.

Methods: *Experiment 1:* Adult female Charles-River rats received olanzapine, 1.2mg/kg, BID or vehicle (control) for 34 days; then received olanzapine, 1.2mg/kg, BID, plus mifepristone, 10mg/kg, 30mg/kg, or 100mg/kg, BID, or vehicle for 21 days.

Experiment 2: Adult female Charles-River rats received olanzapine, 1.2mg/kg, BID, or olanzapine, 1.2mg/kg, BID, plus mifepristone, 10mg/kg, 30mg/kg, or 100mg/kg, BID, for 22 days. In both experiments, animals were dosed via gavage and had ad libitum access to a normal diet and water. Body weight was collected every 3 days and food consumption was measured daily. Abdominal fat was measured at termination.

Results: *Experiment 1*: Weight gain was significantly greater for the olanzapine group ($p<.01$) at day 35. The mifepristone + olanzapine groups lost a significant portion of the weight they had gained on olanzapine alone ($p<.0001$) from day 35-42, and average weights of the groups were not statistically different from controls at study end (day 55).

Experiment 2: The olanzapine group gained significantly more weight compared to the mifepristone + olanzapine groups starting on day 3 ($p=.001$) and continuing through day 22 ($p=.0002$). Olanzapine treated rats had significantly more abdominal fat compared to rats in the mifepristone + olanzapine groups ($p<.0001$). Food consumption was significantly higher for the olanzapine group versus the mifepristone + olanzapine groups ($p=.0003$).

Conclusions: Results suggest that mifepristone mitigates olanzapine-induced body weight gain and abdominal fat deposition in this model.

Session I - 94

Escitalopram for Complicated Grief: A Pilot Study

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Background: Complicated grief (CG) is a recently defined syndrome in which symptoms of acute grief persist for more than six months following the death of a loved one. CG has unique features related to difficulty accepting the death, yearning and longing for the person who died, and preoccupation with thoughts and memories of this person. We developed a targeted psychotherapy (CGT) that performed better than interpersonal psychotherapy for depression in a randomized controlled trial. To our knowledge, there is no reported study of medication alone for patients with this condition. We thus report results of an open pilot study of escitalopram.

Method: Seventeen patients who met our criteria for CG entered a 16-week open treatment study. Participants underwent a baseline assessment including confirmation of the presence of complicated grief on structured clinical interview. Escitalopram was started at 10 mg/day, and increased to 20 mg/day after 4 weeks, at the discretion of the physician. Thereafter, visits were biweekly for 2 months and then monthly. Patients completed the Inventory of Complicated Grief (ICG) at each session. An independent evaluator rated symptoms and CGI on a monthly basis.

Results: Seven patients completed the study and 9 dropped out (2 due to side effects, 1 for exacerbation of a prior physical illness, 6 lost to follow-up). Table 1 shows results for intent-to-treat and completer samples. In the ITT sample, 5/13 (38%) were responders, defined by a CGI score of 1 or 2. This rate is similar to that of CGT alone (42%) in our randomized controlled trial, and both are lower than we observed for patients in the psychotherapy study who were stabilized on antidepressant medication (59%).

Conclusions: A pilot study of escitalopram produced promising results for CG, similar to those seen with CGT. Combined with results from our earlier psychotherapy study, it appears that combination medication and psychotherapy may produce the best outcome for this condition.

Table 1:

Intent to Treat

Variable	Pre treatment	Post treatment	Difference	Effect size
ICG	46.2 (10.1)	34.9 (14.9)	10.7 (9.4)	1.13
HAM D	29.4 (6.3)	24.1 (11.3)	5.3 (9.2)	0.57
SIGH A	21.4 (6.0)	15.9 (6.8)	5.5 (5.9)	0.94

Completers

Variable	Pre treatment	Post treatment	Difference	Effect size
ICG	42.1 (9.7)	27.7 (13.5)	14.4 (9.1)	1.58
HAM D	30.0 (3.6)	19.1 (8.2)	10.9 (8.1)	1.34
SIGH A	22.5 (5.1)	13.4 (4.4)	8.7 (2.6)	3.36

Session I - 95

Nutritional Status of Depressed and Nondepressed Pregnant Women

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Background: Nutritional psychiatry in the perinatal period is an emerging field that holds significant promise for preventing and treating mood disorders and improving offspring health. Nutrients are essential for normal brain function, and may be important in the pathophysiology of major depression. Conversely, nutritional status may be adversely affected by depressive symptoms. Data also suggest that poor nutritional status reduces response to antidepressants. Understanding these associations is particularly important for perinatal women, since pregnancy and lactation are significant nutritional stressors. Nutrient needs are higher during these periods than at any other time in the lifecycle. Our objective was to assess the association between depression and nutritional status during pregnancy.

Methods: At 20 weeks' gestation, depressed and nondepressed pregnant women who enrolled in a longitudinal cohort study provided blood samples that were analyzed for plasma vitamin C, serum folate, and serum carotenoids. Prepregnancy body mass index (BMI) was based on self-reported weight and height. Depression was defined as a SIGH-ADS score>20 or EPDS score>10.

Results: Depressed women (n=49) had significantly higher mean pre-pregnancy BMI values than controls (n=133) [28.3 (SD, 1.1) vs. 25.6 (0.6) kg/m2; $p<0.05$], even after adjusting for race, antidepressant use, and age. Moreover, depressed women were 2.3 times as likely as controls to be classified as overweight (BMI=25; $p<0.05$). In a subsample with plasma analyzed for vitamin C, mean plasma vitamin C concentrations were significantly lower among depressed women (n=16) than controls (n=59) [10.5 (SD, 3.5) vs. 13.0 (3.0) μg/ml; $p<0.05$]. After adjusting for antidepressant use, race, marital status, education, age, and fasting in a multivariable linear regression model, depression was associated with a 2.4 μg/ml reduction in plasma vitamin C ($p<0.01$). Also, depressed women were significantly more likely than controls to be in the lowest third of the plasma vitamin C distribution (46.9% vs. 19.7%, $p<0.001$). Similar trends were observed for serum folate and carotenoids, though not all results reached statistical significance.

Conclusions: Although longitudinal data are needed to establish the temporality of these associations, our preliminary data suggest that nutritional status may be compromised in depressed women during pregnancy. Further investigation of these and other aspects of nutritional status in relation to depression is warranted.

Session I - 96

Development of a Short Version of the Social Adjustment Scale-Self Report

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Background: The assessment of social functioning has become a critical component of therapeutic trials and results can be used to justify both the use of new therapies and the maintenance of old therapies. The Social Adjustment Scale-Self Report (SAS-SR), a 54-item self-report scale, has been found to reliably and validly measure both the level of behavioral and emotional social adjustment across various life role-areas. Specifically, six major role-areas of functioning are covered: work, (paid worker, unpaid homemaker, or student), social and leisure activities, relationships with extended family, role as a marital partner, role as a parent, and role within the family unit. The items within each area cover four content categories: performance at expected tasks; the amount of friction with people; finer aspects of interpersonal relations; and feelings and satisfactions. Comparisons of the SAS–SR with other widely used social functioning scales make it clear that the SAS–SR covers a number of areas that are important but excluded from most scales (e.g., marital and parental functioning and relations with the extended family). However, for some purposes (e.g., pharmaceutical research programs) a shorter version of the SAS–SR was required.

Objective: To develop a reliable and valid abbreviated version of the SAS-SR (SAS-SR: Short) that can be used in clinical and research programs when there is insufficient time to complete the full assessment.

Methods: Nine-hundred fifty-seven (422 men and 535 women) non-clinical participants were recruited by the National Family Opinion household panel as part of a national study of bipolar disorder. The sample was stratified to be representative of U.S. demographics with respect to gender, age, race, household size, income, and census region. The sample was assessed with the SAS-SR via a postal survey. The SAS-SR: Short was developed through a series of reliability, content, and confirmatory factor analyses. The correlation between the full-length SAS-SR and the SAS-SR: Short was subsequently computed. Seventy clinical patients also completed the SAS-SR in order to assess the discriminative validity of the abbreviated scale. Specifically, the clinical patients were matched (on age, gender, and employment status) to 70 participants from the normative sample. A series of discriminant function analyses (DFAs) were conducted in order to determine if the SAS-SR: Short could distinguish between the clinical and non-clinical groups.

Results: In determining which items to retain on the shortened version of the SAS-SR, reliability statistics were examined at both the item and overall scale level. The item-analyses were conducted in a backwards stepwise manner, with the worst items being removed one at a time until the items were finalized. Content analyses were conducted concurrently with the reliability analyses in order ensure that the theory underlying the original SAS-SR was maintained. The content analyses involved ensuring that all six role-areas and all four content areas (i.e., Performance, Interpersonal, Friction, and Feelings) were represented on the shortened scale. These analyses resulted in the multidimensional 24-item SAS-SR: Short, including three items per role-area. Coefficient alpha for the SAS-SR: Short was .87. Confirmatory factor-analytic results revealed that the original 6-factor structure of the SAS-SR held up with the SAS-SR: Short items. The SAS-SR: Short was found to be highly correlated with the original SAS-SR, r = .93, p < .001. Evidence for the discriminative validity of the scale was found as the results of the DFAs revealed that the SAS-SR: Short was able to distinguish between clinical and non-clinical groups. Specifically, the SAS-SR: Short total score correctly classified participants as either clinical or non-clinical 80.0% of the time, sensitivity (i.e., the proportion of clinical patients predicted to belong to the clinical group) was 75.6%, and specificity (i.e., the proportion of non-clinical participants predicted belong to the non-clinical group) was 86.2%. The SAS-SR: Short role-area subscale scores had an overall correct classification rate of 98.1%, sensitivity was 95.8%, and specificity was 100.0%.

Conclusions: The SAS-SR: Short is a reliable and valid measure that can be used as an effective screener of social adjustment.

Session I - 97

Escitalopram Treatment of Pathological Gambling with Co-occurring Anxiety: An Open-Label Pilot Study with Double-Blind Discontinuation

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Background: Although co-occurring disorders are common in pathological gambling (PG), investigation of response to pharmacotherapy in individuals with PG and co-occurring psychiatric symptomatology is limited.

Methods: Thirteen subjects with DSM-IV PG and co-occurring anxiety were treated in a 12-week open-label trial of escitalopram. Subjects were assessed with the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS; primary outcome measure), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impressions scale (CGI), and measures of psychosocial functioning and quality of life. Those subjects who "responded" (defined as a 30% or greater reduction in PG-YBOCS total score at endpoint) were offered inclusion in an 8-week double-blind discontinuation phase.

Results: PG-YBOCS scores decreased from a mean of 22.2 ± 4.5 at baseline to 11.9 ± 10.7 at endpoint (p=.002), and 61.5% were responders. Scores on the HAM-A decreased by 82.8% over the 12-week period (mean of 15.9 ± 3.2 at baseline to a mean of 2.8 ± 3.6 at endpoint) (p<.001). On the CGI, 38.5% of subjects (n = 5) were "very much improved," and 23.1% (n = 3) were "much improved" by study endpoint. The Sheehan Disability Scale, Perceive Stress Scale, and Quality of Life Inventory all showed improvement (p=<.001, p=.002, and p=.029, respectively). The mean end-of-study dose of escitalopram was 25.4 ± 6.6 mg/day. Of three subjects assigned to escitalopram during the discontinuation phase, none reported statistically significant worsening of gambling symptoms. One subject assigned to placebo, however, reported that gambling symptoms returned within 4 weeks.

Conclusions: Open-label escitalopram treatment was associated with improvements in gambling and anxiety symptoms and measures of psychosocial functioning and quality of life. Larger, longer, placebo-controlled, double-blind studies are needed to evaluate further the safety and tolerability of escitalopram in the treatment of PG and co-occurring anxiety.

Session I - 98

Weight Changes Associated with Treatment with Orally Disintegrating Olanzapine

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Introduction: Multiple studies have demonstrated that olanzapine induces significant weight gain. In a meta-analysis of 81 studies, patients gained 9.2 pounds during 10 weeks of treatment. At 12 weeks, an average weight gain of 16 pounds has been reported. This weight gain may be mediated by delayed post-ingestion satiety resulting from antagonism of 5-HT2c, 5-HT3, and H-1 receptors. Recently published data suggest that orally disintegrating olanzapine minimizes weight gain and even induces weight loss. This retrospective naturalistic study analyzes the weight and BMI changes of outpatients treated with orally disintegrating olanzapine.

Methods: A review of patients treated for mood, anxiety, and psychotic disorders at an outpatient psychiatric clinic from May 2005 through November 2005 was performed. Patients 18-65 years old who received treatment with orally disintegrating olanzapine were selected. Individuals previously treated with conventional olanzapine and switched to disintegrating tablets were excluded. Patients concurrently treated with mirtazapine, corticosteroids, or additional antipsychotics were also excluded. Patients were instructed to dissolve the orally disintegrating olanzapine in their mouths at bedtime and remain NPO for >30 minutes thereafter. None of the patients received nutrition or exercise counseling.

Results: A total of 58 patients met criteria for study inclusion (15 men, 43 women). Average treatment time was 77 days. Patients gained an average of 7.5 lbs (P<0.0001), with a BMI increase of 1.25 kg/m2 (P<0.0001). Women gained 8.6 lbs (P<0.0001), while men gained 4.3 lbs (P=0.24). Clinically significant weight gain was seen in 28% of patients (N=16).

Conclusions: Treatment with orally disintegrating olanzapine is still associated with weight gain. However, as compared to studies of conventional olanzapine, orally disintegrating olanzapine may be associated with slightly less weight gain. This finding may be due to increased sublingual absorption, thus reducing olanzapine's exposure to 5-HT and H-1 receptors in the gastrointestinal tract. Further research utilizing a randomized, blinded trial is warranted.

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Session I - 99

Project MED: Medication Education for Consumers with Language Limitations

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Objectives: The goal of Project MED (Medication EDucation) is to provide information on common psychotropic medications that is easily understood by individuals with language limitations (especially those with developmental disabilities). Eight booklets, written on a 4th-5th grade reading level and containing simple illustrations, were produced on Patients' Rights and Responsibilities and various groups of medications: anticonvulsant, antipsychotic, antidepressant, antimanic, antianxiety, stimulant, and "other medicines." The booklets were distributed through clinics, pharmacies, hospitals, and other establishments, along with questionnaires that contained questions on demographics and the effectiveness of the booklets.

Results: Nearly all 604 respondents were satisfied with the booklets, although some subgroups were generally more likely to respond even more favorably and/or to have greater understanding of the contents than others. For example, females (83%) were more likely than males (68%) to understand at least some of the information ($p = .0009$), and more minorities (73%) than Caucasians (48%) reported that they learned "a lot" ($p = .0009$). Participants who had mental retardation and/or developmental disabilities (MR/DD) were generally able to understand, learn from, and often independently read the booklets; 63.7% of these respondents found the booklets easy to understand, and 90.3% indicated that they learned at least "a little" from the booklets. Undoubtedly, the most important hurdle to clear in creating educational tools for individuals likely to have reading difficulties, such as people with MR/DD, is including all of the necessary information while maintaining an accessible reading level. Project MED achieved this goal for most consumers, even those with MR/DD.

Session I - 100

Cardiovascular Risk Parameters in Psychiatric Outpatients

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Background: Atypical antipsychotics can exacerbate coronary heart disease (CHD) risk in psychiatric patients because of their propensity to modify lipid and glucose metabolism. Routine lipid monitoring is recommended, but in those at increased risk, lipid particle sizes and concentrations also should be measuresed. These special assays define a unique CHD risk profile not identified with routine lipid markers.

Methods: Psychiatric outpatients stabilized on their psychotropic regimen were recruited to assess their fasting lipid profile, lipid particle sizes/concentrations, and vital signs. Subjects were chosen regardless of their medication status or comorbidities and represented a naturalistic sample of those attending a university outpatient service. Subjects were classified into several CHD risk categories based on clinical and laboratory parameters. These included the following risk categories: ≥3 of 5 components of the Metabolic Syndrome (MS), non-HDL cholesterol level ≥150mg/dl and LDL particle concentration ≥1300 nmol/L, and the relative risk of the Framingham Coronary Disease Risk Prediction Scores.

Results: The 27 subjects recruited included 21 men and 6 women, mean age 44.7 (SD 10.8) and 43.7 (SD 6.6) respectively. Nearly half met criteria for the MS, 43% (9/21) of men and 50% (3/6) of women. Only mean total and LDL cholesterol in men and only triglyceride (TG) and HDL-C in women clearly met NCEP Guideline goals. Only 15% (4/27) met all four lipid parameter goals. Median, rather than mean, lipid levels are more informative for hyperlipidemia severity. Of the 27 subjects, 11 (7M:4F) had elevated non-HDL cholesterol (≥150mg/dl) and total LDL particle concentration ≥1300 nmol/L. Only 6 of these 11 subjects also met criteria for the MS. This classification identified 5 additional patients at risk for CHD. The Framingham Coronary Disease Risk Prediction scores based on total cholesterol and LDL-C were calculated. A relative risk (RR) score compared each individual's unique CHD risk to the average 10 year CHD risk. Although the mean CHD-RR for CHOL and LDL-C was similar and less than 1.0 (0.82) for men, 24% (5/21) had a RR ranging from 1.14 to 2.0. For women, these parameters were 1.2 and 1.28, respectively. Half (3/6) of women had RR > 1.0 (range: 1.5-2.5).

Conclusions: Among a naturalistically recruited sample of psychiatric outpatient, significant numbers had elevated CHD risk factors. These results suggest that a larger and more diverse patient sample should be studied to further delineate the utility of these markers.

Session I - 101

Cardiac Risk Factors and Schizophrenia: An Analysis of 14,756 Patients Enrolled in an International Comparative Trial of Olanzapine and Ziprasidone

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Background: Ziprasidone has been used to treat schizophrenia since 2000. An outstanding question has been whether its modest QTc-prolonging effect translates to increased risk of cardiovascular events. The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), an open-label, randomized, postmarketing study, has been conducted to address this issue; it will complete enrollment of 18,000 schizophrenic patients from 18 countries in February 2006. The primary endpoint of non-suicide death will be ascertained over the following year.

Methods: A physician-administered questionnaire collected baseline information on demographics, medical and psychiatric history, and concomitant medication use. Data were self-reported by patients or reported by enrolling physicians in naturalistic practice. Descriptive baseline data on 14,756 patients are presented here and will be updated following enrollment completion.

Results: To date, ZODIAC has enrolled over 17,000 patients. Most patients (81.5%) were from the United States or Brazil; baseline mean age was 41.9 years. Of the patients, 54.9% were male and 61.2% were white. Nineteen percent of patients had hypertension, 15.7% had hyperlipidemia, 47.5% currently smoked, nearly two-thirds had a body mass index of 30 kg/m2 or more, and 8.3% had diabetes at baseline. Mean time since schizophrenia diagnosis was 10.8 years and average Clinical Impression Score was 5.1 (range: 1 to 8). One-third of patients had ever attempted suicide. Seventy-one percent of patients were using antipsychotics at baseline. Nearly 80% of patients were using concomitant medications, with 31.5% using antidepressants, 25.2% using anxiolytics, and 19.8% using mood stabilizers. Less than 3% were using antihypertensives or statins.

Conclusions: ZODIAC baseline data suggest that this study population has substantial prevalence of cardiovascular risk factors. Concomitant medications were used frequently, although hyperlipidemia and hypertension may be undertreated.

Session I - 102

Assessing Resilience as a Predictor of Remission in PTSD Patients Treated with Venlafaxine XR or Placebo

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Background: To evaluate resilience as a predictor of remission in patients with posttraumatic stress disorder (PTSD) treated with venlafaxine extended release (XR) or placebo.

Methods: Data were evaluated from a 3-month study and a 6-month study of adult outpatients with a primary diagnosis of DSM-IV PTSD, PTSD symptoms for ≥ 6 months, and 17-item Clinician-Administered PTSD scale (CAPS-SX_{17}) score ≥ 60. Patients were randomly assigned to treatment with flexible-dose venlafaxine XR (37.5 to 300 mg/day) or placebo. In addition to the CAPS-SX_{17}, outcome measures in both studies included the Davidson Trauma Scale (DTS), Sheehan Disability Scale (SDS), and Connor-Davidson Resilience Scale (CD-RISC). Using LOCF values, baseline CD-RISC items predictive of remission (defined as CAPS-SX_{17} ≤ 20) were identified by logistic regression and baseline CD-RISC items predictive of response on the CAPS-SX_{17}, DTS, and SDS (defined as score change from baseline) were evaluated using multiple regression.

Results: For the 3-month study (venlafaxine XR, n=179; placebo, n=179), items 22 ("In control of your life") and 25 ("Pride in your achievements") were significant (P<0.05) predictors of remission. For the 6-month study (venlafaxine XR, n=161; placebo, n=168), items 7 ("Having to cope with stress can make me stronger") and 9 ("Good or bad, I believe that most things happen for a reason") were significant predictors. Items predicting CAPS, SDS, and DTS response were also found, although the items predicting response differed between studies.

Conclusions: A number of CD-RISC items significantly predicted remission and response on clinician- and self-ratings of PTSD, although predictors differed between studies.

Session I - 103

Analysis of a Multinational, Cross-Sectional Survey of Physician Perceptions of Negative Symptoms of Schizophrenia

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Background: In schizophrenia, negative symptoms are associated with poor outcomes, but naturalistic data are needed to determine the extent of the problem. We analyzed data from a multinational survey of physicians to assess their antipsychotic drug prescribing practices and perceptions of negative symptoms. The survey provided information on physicians' motivation for prescribing antipsychotic medications.

Methods: Publicly listed specialists in the United States and five European countries who prescribed antipsychotics for at least 15 patients with schizophrenia within the preceding 3 months were invited to complete a questionnaire concerning their patients' clinical status and therapy.

Results: Data for 6523 patients (85% European) were collected from 872 eligible physicians. Two thirds of the patients were outpatients, 63% were men, most were aged 25–44 years, and 50% were unemployed. Outpatient demographic data were comparable to those of the US-CATIE trial and the outpatient EU-SOHO trial. The unemployment rate for U.S. patients resembled that in the US-CATIE trial. Half of the patients were rated as moderately, markedly, or grossly dysfunctional; 34% and 75% of all patients were taking conventional or atypical antipsychotics, respectively, with use of conventional agents more common in Europe than in the United States. The most frequent negative symptoms were social withdrawal (54%), impoverished thought (39%), blunted affect (38%), apathy or avolition (27%), and anhedonia (24%). Negative symptoms appeared to be more prominent among outpatients than inpatients (78% vs 72%). Main prescription drivers included efficacy for positive symptoms (90%), efficacy for negative symptoms (62%), and tolerability (47%). Physicians reported that inadequate control of symptoms was higher for negative symptoms (71%–77%) than for positive symptoms (47%–60%). Atypical antipsychotics were viewed by the physicians as being less effective against negative symptoms than positive symptoms, but more effective than conventional antipsychotics in controlling negative symptoms. As reported by the physicians, adverse events associated with their patients' current antipsychotic treatment included sedation (22%), weight gain (22%), and extrapyramidal symptoms/parkinsonism (13%). Five hundred seventy-nine patients (9%) were categorized as having predominant negative symptoms. In this patient subset, negative symptoms were more prominent than positive symptoms in terms of occurrence rate, driver of prescription, and inadequate control of symptoms, although use of atypical antipsychotics was similar.

Conclusions: This large, multinational, cross-sectional physician survey involving a naturalistic sample of patients with schizophrenia identified more effective treatment of negative symptoms as a key unmet need, especially in patients with dominant negative symptoms.

Session II - 1

Stimulants and Injury in Children and Adolescents with Attention Deficit/Hyperactivity Disorder

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Background: To assess risk factors for injury among children and adolescents treated with stimulants for attention deficit/hyperactivity disorder (ADHD) and evaluate whether the level of adherence with stimulant medications affects their risk of injury.

Methods: An analysis was performed of pharmacy and service claims data from 2000-2003 California Medicaid (Medi-Cal) focusing on children and adolescents, age 6 to 17 years, who initiate stimulant therapy for ADHD. On the basis of the stimulant Medication Possession Ratio (MPR), patients were partitioned into low (<0.3 MPR), medium (0.3-0.7 MPR), and high (>0.7 MPR) stimulant adherence. Bivariate and multivariate analyses were performed to examine associations of stimulant adherence and other patient characteristics with injury.

Results: In a logistic regression model that controlled for duration of stimulant treatment episode and number of treatment visits for ADHD, children and adolescents with a high stimulant MPR were slightly but significantly less likely to be injured than were those with a low stimulant MPR (Odds Ratio: 0.88, 95% Confidence Interval: 0.80-0.97). In this analysis, risk of injury was significantly greater for adolescents than younger children (1.40, 1.29-1.51); boys than girls (1.18, 1.09-1.27); and children and adolescents with ADHD and comorbid anxiety (1.29, 1.10-1.51) or mood disorders (1.16, 1.06-1.28) than those without these comorbidities.

Conclusions: These findings reveal a profile of injury risk among children and adolescents treated for ADHD and suggest that greater adherence with stimulant therapy may have a protective effect on the risk of injury.

Session II - 2

A Multiple-Dose Pharmacokinetic Study of NRP104/SPD489 (Lisdexamfetamine Dimesylate) Following 7-Day Administration

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Background: NRP104 (proposed generic name: lisdexamfetamine dimesylate) is an inactive prodrug of d-amphetamine that, when converted, is designed to be at least as effective as extended-release amphetamine products in the treatment of attention deficit/hyperactivity disorder (ADHD). The objective of this study was to assess the pharmacokinetics, safety, and tolerability of lisdexamfetamine and resulting d-amphetamine at steady state following multiple daily doses in healthy adults.

Methods: This was an open-label, multiple-dose study (subjects aged 18-55 years). Each subject received lisdexamfetamine 70 mg once daily for 7 consecutive days. All subjects fasted from the evening of day 6 until 4 hours after the last dose on day 7. From day 7 to day 10, the pharmacokinetics of d-amphetamine and intact lisdexamfetamine were assessed at 17 time points. The safety data consisted of adverse events (AEs) and vital signs at each visit, and ECG and clinical laboratory test at screening and on day 10 or early termination.

Results: Eleven of 12 subjects (8 women, 4 men; mean age, 37.0 years) completed the study. Daily doses of lisdexamfetamine 70 mg produced steady state concentrations of d-amphetamine by day 5. Elimination of intact lisdexamfetamine was complete approximately 6 hours post dose. At steady state, the mean values for d-amphetamine and intact lisdexamfetamine were, respectively: AUC_{0-24} (ng•h/mL), 1113 and 60.66; AUC_{0-inf} (ng•h/mL), 1453 and 61.06; C_{max} (ng/mL) 90.1 and 47.9; and T_{max} (h), 3.68 and 1.14. All but one AE were mild to moderate in severity, and were similar to those seen with other amphetamine products. The most common AEs were anorexia, insomnia, tachycardia, hyperkinesia, abdominal pain, euphoric mood, headache, and upper respiratory tract infection. After one dose of lisdexamfetamine 70 mg, one female subject was withdrawn from the study due to tachycardia. There were no clinically significant ECG abnormalities.

Conclusions: Single daily doses of lisdexamfetamine 70 mg administered to healthy adults produced steady-state concentrations of damphetamine by day 5, with complete elimination of intact lisdexamfetamine by approximately 6 hours post dose. Lisdexamfetamine 70 mg was well tolerated in adults, producing AEs consistent with those of amphetamine products.

Source of Funding: New River Pharmaceuticals, Inc. and Shire Pharmaceuticals, Inc.

Session II - 3

Pharmacokinetics of NRP104/SPD489 (Lisdexamfetamine Dimesylate) Following Administration of Single Intranasal Dose in Rats

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Background: Stimulant medications are first-line treatments for attention deficit/hyperactivity disorder (ADHD), with a well documented history of efficacy and safety. However, there are concerns about misuse and diversion of these drugs. NRP104 (proposed generic name: lisdexamfetamine dimesylate), an inactive, orally administered amphetamine prodrug composed of d-amphetamine conjugated with L-lysine, was designed to have at least comparable efficacy and safety to extended-release amphetamine products in the treatment of ADHD, with a reduced abuse potential as it needs to be hydrolyzed to release the active component. As lisdexamfetamine is an orally administered capsule, it could potentially be misused by intranasal (IN) administration. In general, the potential for a stimulant to produce a pleasurable effect and its likelihood for abuse depends in part on its pharmacokinetics (i.e., the higher the AUC and Cmax and shorter the Tmax, the greater the potential for abuse). The objective of this study was to assess the pharmacokinetics and bioavailability of lisdexamfetamine and resulting d-amphetamine following administration of a single IN dose in rats.

Methods: Single IN boluses of lisdexamfetamine or d-amphetamine sulfate were administered to groups of four male Sprague-Dawley rats at a dose of 3 mg (d-amphetamine base)/kg. Following administration, plasma samples were collected at 5, 15, and 30 minutes, and 1 hour, and analyzed for d-amphetamine and lisdexamfetamine pharmacokinetics.

Results: Following IN administration, pooled plasma results showed that the d-amphetamine pharmacokinetics differed substantially between lisdexamfetamine and equimolar d-amphetamine sulfate. With lisdexamfetamine, the d-amphetamine AUClast was about 95% less (56 vs 1032 ng•mL/h), Cmax about 96% less (78.6 vs 1962.9 ng/mL), and Tmax 12 times longer (1 vs 0.083 hours). The analysis also showed a high concentration of intact lisdexamfetamine (AUCinf, 9,139 ng•mL/h; Cmax 3345.1 ng/mL).

Conclusions: Compared with IN d-amphetamine sulfate, IN lisdexamfetamine, a prodrug, substantially decreased and delayed the bioavailability of d-amphetamine. After administration of lisdexamfetamine, the concentration of this prodrug remained high and the concentration of d-amphetamine low. These results probably reflected the prodrug's gradual hydrolysis. It appears that the amount of d-amphetamine that can be delivered by IN administration is minimal.

Session II - 4

Methylphenidate Effects on Objective Measures of Activity and Attention Accurately Identify Doses Associated with Optimal Clinical Response

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Background: Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent neuropsychiatric disorder that can respond dramatically to medication. However, children are often under-treated, and rarely receive the type of benefit medications can provide (MTA Cooperative Group, 1999). Laboratory measures of attention are responsive to stimulants, but some studies suggest that continuous performance tests (CPT) cannot be used for titration as CPT performance improves on doses too low to produce clinical benefits (Matier et al., 1992). We sought to ascertain whether objective assessment of motor activity and attention could identify methylphenidate (MPH) doses associated with optimal clinical response.

Methods: Eleven Caucasian boys (9.6 ± 1.8 years of age; range: 6-12) currently receiving treatment with MPH, and meeting DSM-IV criteria for ADHD, participated in this IRB-approved randomized order, triple-blind (parent, child, rater), within-subject, treatment trial. Subjects received one week each of placebo, low (0.4 mg/kg), medium (0.8 mg/kg) and high (1.5 mg/kg) daily doses of MPH administered bid. During the last day on each regimen, children were tested objectively for degree of hyperactivity and inattention. Parents rated weekly response using an index of clinical global improvement (CGI).

Results: In 10/11 instances, the dose that produced the best overall improvement on objective measures of activity and attention was also the dose rated best by parents ($p < 10\text{-}6$). Similarly, 8/11 parents indicated that their child's worst week occurred in concordance with their worst objective outcome ($p=0.00001$). Parents rated the week that produced the best overall improvement in objective response as significantly better than the child's response to their customary treatment (CGI: +1.64, 95% CI: 0.58-2.69). The week producing the poorest objective response was rated as significantly worse than customary treatment (CGI: –1.55, 95% CI: –0.73 to –2.36), and the differences between these weeks was highly significant ($F_{1,10}=25.52$, $p<0.0005$).

Conclusions: Objective measures of activity and attention responded to treatment in a matter that was highly concordant with parent ratings of clinical response, and in 91% of cases identified the dosage parents rated as most beneficial. This suggests that office-based assessment of clinical response, using objective measures of activity and attention, has ecological validity, and the potential to facilitate rapid and accurate dose titration.

Session II - 5

Conducting Long-Term Studies: Observations from a Functional Outcome Study for Adult Attention Deficit/Hyperactivity Disorder (ADHD)

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Background: Recent emphasis in pharmacological research has been to assess the efficacy of interventions not only for reducing symptom severity, but also for improving patients' functional outcomes. However, the complex interplay between psychiatric illness and role functioning suggests that longer treatment periods may be necessary to demonstrate the optimal impact of interventions. In the present study, we examined work productivity in adults with attention deficit/hyperactivity disorder (ADHD) following 6-month treatment with either atomoxetine (ATX) or placebo (PBO). As illustrated by our findings, longer-term, double-blind, randomized treatment studies present several design challenges.

Methods: Patients were 410 adults who had ADHD established by the Connors' Adult ADHD Diagnostic Interview for DSM-IV, were employed for at least 20 hours/week for 6 months, and had a Clinical Global Impressions Severity rating ≥4 "moderate" at baseline. The primary measure was the Endicott Work Productivity Scale (EWPS) total score. To parallel clinical settings, visits were spaced so that patients had four clinic and two phone visits over 6 months.

Results: The sample was predominantly male (58.5%); mean age=36.8 yrs, range 18.5-50; ATX, *N*=271, and PBO, *N*=139. Substantial attrition occurred, with an overall completion rate of 42%. Main reasons for discontinuation were loss to follow-up (15.6%), lack of efficacy (11.0%), patient decision (10.5%), and adverse events (10%). Groups did not differ in these discontinuation reasons, except for adverse events (ATX group=14% vs. PBO group=2%, *P*<.001). There was also a high placebo response rate. At 6 months, both groups had similar, nonsignificantly different improvements in EWPS total scores. Post-hoc subgroup analysis showed a trend for a treatment-by-age interaction (*P*=.057). For young adults (ages 18-30), mean reduction in impairment on EWPS was 19.4 for the ATX group versus 10.4 for the PBO group, *P*=.01.

Conclusions: The attrition and placebo rates affect the interpretability of the study. Although naturalistic, low-visit frequency may have contributed to poorer research participation as indicated by the rate of "loss to follow-up". One reason for the high placebo rate could have been the lack of an independent disease-specific severity entry criterion. Also, childhood diagnosis was determined from patient self-report rather than from a corroborative third party, such as a parent. Thus, the diagnosis of older patients may have been more circumspect. Observations from the present study support the need to consider visit frequency and entry stringency in the design of longer-term randomized trials.

Session II - 6

Modafinil-ADHD in Children and Adolescents with Attention Deficit/Hyperactivity Disorder: Efficacy and Tolerability Is Maintained with Long-Term Treatment

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Background: Modafinil-ADHD improves ADHD symptoms and is well tolerated in children and adolescents in studies lasting up to 9 weeks. We evaluated the long-term efficacy and tolerability of modafinil-ADHD in these patients.

Methods: Patients (aged 6–17 years) were enrolled in a 12-month, open-label study of modafinil-ADHD (170–425 mg once daily). Efficacy was assessed using the ADHD Rating Scale-IV (ADHD-RS-IV) Home Version, which consists of 18 items scored on a 4-point scale (0=never/rarely; 1=sometimes; 2=often; 3=very often), with a maximum score = 54. Improvement in ADHD symptoms is reflected by a decrease in score. Clinicians rated the severity of illness of the patient using the Clinical Global Impression of Severity (CGI-S), with scores ranging from 1 (normal/not at all ill) to 7 (among the most extremely ill). Patient-reported adverse events (AEs), vital signs, and laboratory tests were also evaluated.

Results: Of 536 patients enrolled, 533 were included in the safety analysis set (73% boys; mean age, 10 years; mean weight, 42 kg) and 505 in the full analysis set; 237 patients completed the 12-month study (completer population). Modafinil-ADHD improved mean scores on the ADHD-RS-IV Inattention and Hyperactivity-impulsivity subscales and the Total score among patients in the full analysis set and among completers (Table). Responders (i.e., percentage of patients who experienced ≥1-point reduction from baseline in the CGI-S) were 78% in the full analysis set and 93% in the completer population. Seven percent of enrolled patients withdrew because of AEs. The most commonly reported AEs in the full analysis set and completer populations were infection (22% and 34%, respectively), headache (21% and 28%), insomnia (26% and 24%), increased cough (11% and 19%), and decreased appetite (13% and 14%). Most AEs in both patient populations were mild to moderate in severity. There were no notable changes in vital signs or laboratory values in either group.

Conclusions: Modafinil-ADHD improved ADHD symptoms and was well tolerated in children and adolescents with ADHD for up to 12 months.

Table. Results for ADHD-RS-IV Home Version

	Full Analysis Set (n=505) Mean (SD)			Completers (n=237) Mean (SD)		
	Baseline	Final Visit	Change	Baseline	Final Visit	Change
Inattention subscale	21.8 (4.5)	12.4 (7.2)	–9.4 (2.3)	21.6 (4.5)	9.4 (5.4)	–12.2 (6.0)
Hyperactivity-impulsivity subscale	17.1 (7.0)	8.5 (7.1)	–8.5 (6.9)	16.5 (7.2)	5.7 (4.8)	–10.8 (6.3)
Total	38.9 (9.3)	21.0 (13.1)	–17.9 (12.7)	38.1 (9.4)	15.1 (8.9)	–22.9 (10.4)

Session II - 7

Children with ADHD Have Multi-Second Spike-Wave Bursts of Movement During a Vigilance Task That Are Suppressed by Methylphenidate

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Background: The hyperactivity of children with attention deficit/hyperactivity disorder (ADHD) is most readily discernible as a failure to inhibit motor activity to low-levels. Teicher et al (1996) precisely quantified movements of ADHD children and found that they were 3-4 fold more active than controls. However, the precise nature of their hyperactivity is unknown. We sought to ascertain whether ADHD children move continuously or episodically, and whether stimulants reduce activity by attenuating movement amplitude or altering temporal patterns.

Methods: Sixty-two boys (10.6±1.1 years of age, range 9-12) meeting DSM-IV criteria for ADHD participated in this IRB-approved study. Head movements were recorded prior to, and following, a probe dose of 0.4 mg/kg methylphenidate, while subjects were seated and performing a Go/No-Go CPT. An infrared motion analysis system tracked and recorded vertical and horizontal position of a head marker 50 times per second to a resolution of 0.04 mm.

Results: ADHD children had episodic bursts of movement, which occurred as discrete spikes. Across spike amplitude threshold children with ADHD had from 2X (low threshold) to 44X (high threshold) more spikes off medication (MPH effect: $F_{1,61}=73.87$, $p<10^{-11}$). Spikes had a typical amplitude of between 1.6 and 6.4 mm, mean duration of 240 msec, and an interspike interval of 10–100 seconds (x = 26.0 sec). MPH increased ISI by 2-4 X (e.g., 2 mm threshold, ISI 14.5±23.5 vs. 43.0±56.8 sec, $F_{1,39}=8.82$, $p<0.005$).

Conclusions: Prior to treatment, about 25% of the activity of ADHD children occurred as discrete spikes. MPH reduced this by 80% by markedly attenuating number of spikes and increasing interspike intervals. Interestingly, Allers et al., (2002) have shown that basal ganglia neurons of rats have multi-second spike trains with similar temporal properties (20-35 sec), and respond in the same way to stimulant drugs. This supports Castellanos et al., (2005) hypothesis that ADHD may be related to a disturbance in low frequency oscillations that result in fluctuations in attention and bursts of activity.
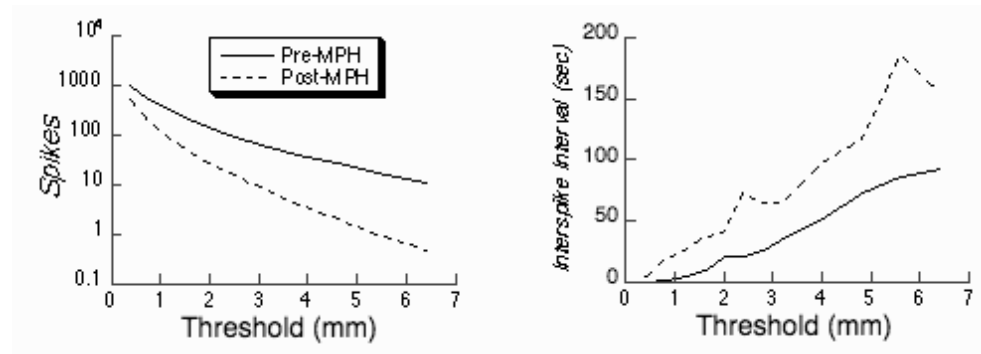
Session II - 8

A Pilot Study for Augmenting Atomoxetine with Methylphenidate: Safety of Concomitant Therapy in Children with Stimulant-Resistant Attention Deficit/Hyperactivity Disorder (ADHD)

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Background: Augmentation strategies and concomitant pharmacotherapy have become common in pediatric pharmacology despite a dearth of empirical studies to support their safety. The present study examined the safety and efficacy of augmenting atomoxetine (ATX) with extended-release methylphenidate (MPH) in the treatment of children with attention deficit/hyperactivity disorder (ADHD) who had previously failed stimulant treatment.

Methods: Twenty-five children met the inclusion criteria of a primary diagnosis of DSM-IV ADHD, prior history of nonresponse to an adequate trial of a stimulant, and at least moderate severity of illness. All but one patient (who withdrew) received treatment with ATX (target dose of 1.4 mg/kg/day) and placebo (PBO) for 4 weeks. Mean age of this sample was 9.6 year (83% male). Patients whose ADHD remitted after 4 weeks were continued on ATX and placebo. The remaining patients with continued ADHD symptoms were randomly assigned to ATX plus either blinded MPH or PBO. Patients were seen for six visits over 10 weeks of treatment. Safety measures included vital signs, weight, and adverse-event reports. Efficacy was assessed using the ADHD Rating Scale for DSM-IV Parent report Investigator Rated (ADHDRS-IV-Parent:Inv), Connors' Parent Rating Scale-Revised (CPRS-R), and the Clinical Global Impressions Severity and Improvement (CGI-S, CGI-I).

Results: Of the 25 children, 4 discontinued the study prior to randomization; 4 remitted during the initial ATX 4-week treatment and were not randomly assigned; 9 were randomly assigned to MPH; and 8 were randomly assigned to PBO. There were no significant adverse events. Patients in the combined treatment had a statistically significant decrease from baseline for Body Mass Index (-.86 kg/m2, P=.01) and for diastolic blood pressure (-3.6 mm HG, P=.01). The most frequent AEs were vomiting, nausea, initial insomnia, and headache. An overall treatment response to ATX was found [ADHDRS-IV-Parent:Inv mean change baseline to 4 weeks =-17.8, P<.001; CPRS-R mean change=-17.1, P<.001; CGI-S mean change=-1.5, P<.001], but the addition of MPH did not further enhance this response.

Conclusions: This small pilot study suggests that MPH can be safely combined with ATX, but more research is needed, and there is no evidence of a group benefit from the combination in patients who have failed an adequate trial of stimulants. Consistent with prior studies, approximately 20% of children who had failed to respond to stimulants experienced remission in their ADHD with atomoxetine treatment.

Session II - 9

Neuropsychological Functioning and OROS Methylphenidate in an Adult Attention Deficit/Hyperactivity Disorder (ADHD) Population

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Background: Neuropsychological tests have been used in attention deficit/hyperactivity disorder (ADHD) to compare ADHD patients to normal subjects, to assess drug-placebo differences in clinical trials, and to identify appropriate medication levels via test dose paradigms. While clinical studies have generally been positive with moderate effect sizes, outcomes have been inconsistent, particularly in adults. This analysis examined a neurocognitive battery in a sample of adult ADHD subjects during a clinical trial of OROS methylphenidate (MPH).

Methods: This 8-week crossover study utilized OROS MPH in 41 subjects who met DSM-IV criteria and the Utah Criteria for ADHD. ADHD symptoms were assessed using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (Reimherr et al 2003) and the ADHD Rating Scale. The CNS Vital Signs (CNS-VS) is a computer-based neurocognitive battery with tests of verbal and visual memory, finger tapping, symbol-digit coding (SDC), the Stroop test, the shifting attention test (SA), and the continuous performance test (CPT). The developer has reported average scores for both normal and ADHD subjects on these tests. Baseline scores on this population were compared with the normative data. The impact of treatment (OROS MPH versus placebo) on test scores was assessed via paired t-tests.

Results: OROS MPH proved superior to placebo for all clinical ADHD measures, including total WRAADDS (44% versus 13% improvement, p=.006), plus the subscales addressing inattention, hyperactivity/impulsivity, and emotional dysregulation. At baseline our ADHD patients had CNS-VS scores midway between the developer's ADHD and normal samples. However, on reaction times on the CPT, Stroop, and SA and errors in the Stroop and SA tests, our patients scored worse than either comparison group. While OROS MPH was usually associated with better scores than placebo, this difference only achieved significance for four of the tests: SDC (p=.041), Stroop Complex Reaction Time (p=.009), SA Number Correct (p=.018), and CPT Reaction Time (p=.034).

Conclusions: Baseline scores were consistently worse than the test developer's normative data, and endpoint scores on OROS MPH were consistently better than placebo. The tests that reached or approached significance were all test scores that had previously reached significance in test dose paradigms. The longer period between testing in this clinical trial (4 weeks) compared to a test dose paradigm (1 hour) may contribute to the weaker relationship. Conversely, actual clinical trials in adults with ADHD have frequently failed to find drug-placebo differences on cognitive testing.

Session II - 10

Combined OROS MPH and Atomoxetine in ADHD Treatment in Children

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Objective: Despite the use of combined atomoxetine (ATMX) and stimulant, there are no prospectively collected data demonstrating either efficacy or tolerability of the combination. The aim of the study was to evaluate the efficacy and safety/tolerability of adding OROS-MPH (CONCERTA) to children who have had at least mild ADHD symptoms on ATMX for ADHD.

Method: This is an ongoing, two-phase, 7-week open-label study in patients aged 6 to 17 years. Phase one initiates ATMX for a minimum of four weeks. Phase two enters ATMX partial responders and adds OROS-MPH to their regimen. Subjects are assessed on multiple outcomes, including ADHD-RS (rating scale), executive functioning, and adverse effects.

Results: At midpoint, 33 subjects were exposed to ATMX and 22 subjects entered into Phase II. Overall, there was a 60% reduction in the ADHD-RS from pre-drug baseline to end of study. The addition of OROS-MPH to ATMX resulted in a 32% drop in ADHD symptoms ($p < 0.0001$). In addition, there were clinically significant reductions in CGI-Severity from moderate to mild ADHD (23%, $p < 0.0001$), improvements on CGI after Phase I (59%) and Phase II (67%), and improvements in executive functioning. There were no serious adverse events; however, side effects appear to be additive, with headache, nausea, insomnia, appetite loss, and lethargy most commonly reported on the combination.

Conclusions: These preliminary results suggest that OROS MPH added to partial responders of ATMX improves ADHD and executive functioning and is well tolerated.

Session II - 11

Acamprosate Decreases the Severity and Duration of Relapse and Aids in Post-Relapse Recovery of Abstinence in Alcohol-Dependent Patients

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Background: A major goal of alcohol-dependence treatment is relapse prevention. Acamprosate, with psychosocial support, is effective in helping alcohol-dependent patients maintain abstinence and regain abstinence following relapse. In the current analysis, we examined the effect of acamprosate on the severity of relapse in patients who returned to drinking and assessed their post-relapse recovery.

Methods: The intent-to-treat (ITT) population from three double-blind, placebo-controlled, multicenter, pivotal trials (13-, 48-, and 52-weeks) in which patients received acamprosate 1998 mg/day (n=372) or placebo (n=375), in combination with psychosocial therapy, was evaluated for the quantity of alcohol consumption during relapse (at Day 0, 30, 60, 90, and last visit). Weekly frequency of alcohol consumption (13-week study) and duration of individual relapse episodes (48-week study) were also reported. In an ITT population subset with = 1 documented relapse before last study visit, the rate of complete abstinence, percent days abstinent, and time to first drink were analyzed on abstinence periods following a relapse.

Results: Of 747 patients, 616 relapsed over the course of the studies (placebo, 89%; acamprosate, 76%). Post-relapse recovery was evaluated in patients who relapsed before the last study visit (n=587). Pooled data show that a significantly smaller proportion of acamprosate- than placebo-treated patients reported consuming >5 standard drinks per day during the interval preceding Day 30, 60, 90 and last study visit (p<0.01). Acamprosate was statistically superior to placebo (p<0.05) with respect to frequency of alcohol consumption during relapse (13-week study) and relapse duration (48-week study). A significantly greater proportion of patients treated with acamprosate than placebo regained abstinence following initial relapse and maintained it for the remainder of the trial (13% vs. 5%, respectively; p<0.001).

Conclusions: In addition to helping alcohol-dependent patients maintain abstinence, acamprosate reduces relapse severity in patients who return to drinking and aids in abstinence recovery.

Session II - 12

Randomized, Placebo-Controlled Trial of Quetiapine for the Treatment of Alcohol Dependence

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Background: New atypical antipsychotics may prove to be a significant pharmacotherapy to add to counseling in treating alcohol dependence in certain alcoholic patient populations. Existing published trial data have shown that clozapine reduces alcohol consumption among schizophrenic patients, and olanzapine reduces alcohol craving in alcoholics.[1,2] Quetiapine is a psychotropic agent structurally related to clozapine but with a favorable side effect profile, and the present data demonstrate that it may be a promising medication for the treatment of alcohol dependence. This is the first controlled study completed that evaluated quetiapine for treating alcohol dependence in patients without another major mental disorder.

Methods: Male and female alcoholics (n=61, age 25-64 years) were included in a 12-week placebo-controlled trial. After detoxification, patients were randomized to receive quetiapine (n=29), escalated over 9 days up to 400 mg daily at bedtime, or placebo (n=32), with weekly counseling. The primary outcome measure was alcohol drinking (any and heavy) measured in standard drinks per day by the Timeline Follow-back.

Results: Forty-seven subjects (77%) completed the trial, with no significant between-group difference in treatment retention (23/29 [79%] for the quetiapine group, and 24/32 [75%] for the placebo group; χ^2=0.160, ns). Quetiapine-treated patients (mean dose 303 mg) significantly reduced their alcohol use (group by time interaction: Z=2.2, P=0.03) and amount of heavy drinking, defined as four or more drinks a day for women and five or more for men (Z=2.6, P=0.01), compared to placebo-treated patients. Nine quetiapine-treated patients (31%) compared to two placebo-treated patients (6%) maintained complete abstinence throughout the trial (χ^2=6.3, P=0.012). Quetiapine was well tolerated, and there were no medication-associated serious adverse events. There was also a significant interaction between quetiapine and alcohol subtype, with quetiapine-treated Type B alcoholics (terminology from Babor) reporting less craving for alcohol and less heavy drinking, compared to placebo-treated Type B alcoholics.

Conclusions: This preliminary study shows promising results for quetiapine with counseling in treating alcohol dependence.

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Session II - 13

Substance Use Disorder Comorbidity in Major Depressive Disorder: A Confirmatory Analysis of the STAR*D Cohort

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Abstract: The demographics and clinical features were compared between those with (29.4%) and without concurrent substance use disorder (SUD) in 2541 outpatients with major depression (MDD) enrolled in the Sequenced Treatment Alternatives to Relieve Depression study. Compared to those without SUD, MDD patients with concurrent SUD were more likely to be younger, male, divorced or never married, at greater current suicide risk, and have an earlier age of onset of depression, greater depressive symptomatology, more previous suicide attempts, more frequent concurrent anxiety disorders, and greater functional impairment (p=0.048 to <0.0001). They were also less likely to be Hispanic and endorse general medical comorbidities (p=0.006 and 0.035, respectively).

Session II - 14

Cognitive Function and Acute Sedative Effects of Risperidone and Quetiapine in Patients with Stable Bipolar I Disorder: A Randomized, Double-Blind, Crossover Study

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Background: A double-blind 2x2 crossover study compared effects of risperidone and quetiapine on cognition and sedation in adults with stable bipolar I disorder.

Methods: At each of two 2-day study periods, 15 of 30 patients were randomized to treatment sequence risperidone–quetiapine and 15 to quetiapine–risperidone. Patients received 2mg of risperidone with dinner on day 1, or 100mg of quetiapine with dinner on day 1 and 100mg with breakfast on day 2. Patients were tested at 10 a.m. on day 1 (baseline assessment) and at 10 a.m., 12:30 p.m. and 3 p.m. on day 2 of each study period. A neurocognitive composite score (NCS) was derived from eight computerized tests of processing speed, attention, memory, and executive function. Patients also rated treatment effects on fatigue (sedation) and vigor.

Results: Both periods were completed by 28 of the 30 patients. Between-treatment differences in NCS were significant ($P < 0.05$) at all post-dose assessments, showing improved cognitive functioning after risperidone and deterioration after quetiapine at the two initial post-dose tests (standardized effect xize=1.05). Significant advantages for risperidone relative to quetiapine were found in processing speed and attention. Quetiapine treatment was associated with significantly more fatigue and less vigor compared with risperidone. Adverse events were reported in more patients after quetiapine than risperidone ($P < 0.05$); somnolence was reported in nine patients after risperidone and 24 after quetiapine.

Conclusions: Substantial differences between risperidone and quetiapine were found on neurocognitive function and sedation in patients with bipolar I disorder after initial treatment.

Session II - 15

Bipolar Disorder and Menstrual Cycle Mood Changes:
Are They Related?

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Background: Bipolar disorder is a chronic, episodic, and debilitating illness with a prevalence rate of 3.9%. Though prevalence of bipolar disorder is about the same across gender, literature suggests the course may differ. The rapid cycling course is 3 to 4 times more common in women than men. A complete understanding of issues contributing to these gender differences is unknown; significant numbers of case reports have indicated the possibility of hormonal influences in relation to the menstrual cycle. A handful of studies demonstrate conflicting findings in a systematic analysis of this relationship. Our primary aim is a systematic approach to evaluate if there is a relationship between bipolar disorder and mood changes across different phases of the menstrual cycle in a cohort of women with bipolar disorder.

Methods: Our study population is a cohort of women with bipolar disorder followed intensively in the Stanley Foundation Bipolar Network (SFBN) at the Dallas site. The longitudinal assessment used in the network was the NIMH-Life Chart Method-p (NIMH-LCM-p), which is a daily prospective life charting of mood and associated functional impairment. Daily mood ratings of depression and mania were collected on 38 women who reported the menstrual cycle days for a minimum of 3 consecutive months. Retrospective analyses were done on prospectively collected data from women with bipolar disorder and their mood across different phases of menstrual cycle.

Results: The menstrual cycles were normalized across the 38 women with 3 months of mood data. The cycles were divided into four blocks corresponding to early- and late-follicular and luteal phases, respectively. The mean and standard deviation of the mood data collected from these four phases were analyzed using repeated measures of ANOVA. The results showed no significant changes in mood in any phase of cycle and no trends noted in mood changes. Subsequent analyses using additional variables, such as age and rapid cycling, found no differences across menstrual cycle.

Conclusions: The final analysis of data collected on 38 women did not show any relationship between mood changes across different phases of menstrual cycle and their underlying course of bipolar illness. Our study result is similar to Leibenluft et al study (1999) and this finding is confirmatory in a larger sample of women with bipolar disorder.

Session II - 16

A Randomized, Double-Blind, Parallel-Group Trial of Twice-Daily and Once-Daily Extended-Release Carbamazepine in Bipolar Disorder: Analysis of Safety and Tolerability

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Background: While twice-daily treatment (bid) with carbamazepine extended-release capsules (CBZ-ERC) (Equetro™; Shire, Wayne, PA) has been shown to provide significant therapeutic benefit to patients with acute bipolar mania, retrospective findings suggest that once-daily dosing of CBZ-ERC may be similarly beneficial. Thus, the current study was undertaken to compare prospectively once-nightly (qhs) CBZ-ERC dosing with bid dosing in patients with bipolar disorder.

Methods: All participants in the current 12-week, double-blind trial were adult outpatients experiencing either an acute manic or mixed bipolar episode at study entry. At baseline, study participants were randomized to treatment with either bid or qhs CBZ-ERC. In both treatment groups, patients received a total CBZ-ERC dose of 200 to 1600 mg/d, with optimal doses determined via dose titration over the first 4 weeks post-baseline. Safety and tolerability were assessed at weeks 1, 2, 3, 4, 6, 8, and 12.

Results: Treatment with CBZ-ERC was relatively safe and well tolerated in both treatment groups, with most treatment-related adverse events being mild or moderate. Among the most common adverse events (≥10% incidence) in both treatment arms (bid, n = 53; qhs, n = 58) were nausea (bid, 30.2%; qhs, 24.1%), dizziness (bid, 24.5%; qhs, 17.2%), headache (bid, 22.6%; qhs, 24.1%), sedation (bid, 15.1%; qhs, 12.1%), and blurred vision (bid, 9.4%; qhs, 10.3%). Fatigue (bid, 17.0%; qhs, 6.9%), somnolence (bid, 15.1%; qhs, 8.6%), and increased appetite (bid, 11.3%; qhs, 3.4%) were more common among bid-treated patients when compared with qhs-treated patients, whereas rates of emesis (bid, 3.8%; qhs, 12.1%) and dry mouth (bid, 11.3%; qhs, 17.2%) were higher in the qhs arm than in the bid arm. No serious treatment-related rashes, blood dyscrasias, or cardiac abnormalities were reported. With regard to metabolic adverse effects, 0% and 3.4% of bid- and qhs-treated patients, respectively, reported weight gain, while mean nonfasting serum total cholesterol levels increased in both treatment arms between baseline and endpoint (bid, +18.1 mg/dL; qhs, +12.5 mg/dL).

Conclusions: Carbamazepine extended-release capsules, whether administered using a bid or a qhs dosing schedule, were safe and well tolerated among patients experiencing acute manic or mixed bipolar episodes. Furthermore, metabolic parameters were generally not dramatically affected by CBZ-ERC therapy.

Equetro is a trademark of Shire LLC.

Session II - 17

Metabolic Safety in an Open-Label Study of Extended-Release Carbamazepine Combination Therapy for Patients with Bipolar Disorder

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Background: Polypharmacy is a common practice in the treatment of bipolar disorder, and as a result, systematic characterization of the effects of treating bipolar disorder with multiple agents simultaneously is vitally important. To that end, the current trial was conducted to evaluate the safety of carbamazepine extended-release capsules (CBZ-ERC) (Equetro™; Shire, Wayne, PA) in combination with other psychotropic agents in patients with bipolar disorder. Here, the effects of CBZ-ERC–containing combination therapy on metabolic safety in this trial are discussed.

Methods: The current trial was an 8-week, open-label study involving adult outpatients who were experiencing an acute manic or mixed bipolar episode and who were receiving antipsychotic monotherapy (olanzapine, risperidone, quetiapine, or aripiprazole) or combination therapy involving a mood stabilizer (lithium, valproate, or lamotrigine) plus an antipsychotic at study entry. At baseline, treatment with CBZ-ERC 200 mg/d was initiated, and dose titration (dose range, 200-1600 mg/d) was conducted over the next 4 weeks. During this 4-week period, doses of concomitant mood stabilizers other than lithium were tapered, so that all patients were receiving either CBZ-ERC plus lithium plus an antipsychotic or CBZ-ERC plus an antipsychotic only by the conclusion of dose titration. Following CBZ-ERC dose titration, lithium and/or antipsychotic doses were adjusted as clinically indicated to account for the addition of concomitant CBZ-ERC, and stable doses of CBZ-ERC combination therapy were subsequently administered for the remainder of the study. Safety and efficacy were assessed at weeks 1, 2, 3, and 4, and also at endpoint.

Results: The final study population comprised 53 patients, 49 of whom were receiving antipsychotic monotherapy at baseline. In general, the addition of CBZ-ERC to patients' baseline treatment regimens had minimal metabolic adverse effects, with treatment-related weight increases reported in two patients (3.8%) over the course of the study. Additional treatment-emergent metabolic/nutritional abnormalities included moderate hyponatremia (n = 1 [possibly treatment-related]), mildly increased appetite (n = 1 [possibly treatment-related]), and mild hyperlipidemia/mildly increased blood glucose levels (n=1 [not treatment-related]). No other treatment-related metabolic adverse events were documented.

Conclusions: Results from the current open-label study suggest that the addition of CBZ-ERC to ongoing pharmacotherapeutic regimens has minimal effects on metabolic parameters in patients with bipolar disorder.

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Session II - 18

Metabolic Syndrome Awareness Among Psychiatrists Treating Bipolar Disorder: Results of a National Harris Interactive Survey

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Background: Metabolic syndrome is defined as a constellation of risk factors, including abdominal obesity, insulin resistance, high blood pressure, elevated triglycerides, and below normal high-density lipoprotein, that are associated with increased risks of medical comorbidity. These risk factors may be even more prevalent among patients with psychiatric disorders, including bipolar disorder. A nationwide survey was conducted among practicing U.S. psychiatrists to assess awareness of these metabolic issues and implications for clinical management of bipolar disorder.

Methods: The survey questionnaire was developed by experts in psychiatry and endocrinology. Survey implementation, data collection, and tabulation were conducted by Harris Interactive, Inc. In November 2005, 10,000 psychiatrists were randomly selected from the AMA database, recruited via direct mail, and offered an honorarium to complete the on-line questionnaire anonymously.

Results: Respondents (n=500) have practiced for an average of 15.8 years and saw an average of >70 patients with bipolar disorder in the last month. The majority (94%) believe that metabolic syndrome poses a significant health risk that warrants monitoring and treatment. Many respondents (76%) have formally diagnosed metabolic syndrome, and >80% identify abdominal obesity, hyperglycemia, and hypertriglyceridemia as components of the syndrome. Before initiating treatment, many collect personal and family history of diabetes (83%) and cardiovascular disease (76%), but only about 50% obtain glucose and lipid levels. During ongoing treatment, weight is monitored by 78%; plasma glucose, 69%; lipids, 61%; and blood pressure, 52%. Few treat metabolic abnormalities themselves; most recommend diet and exercise, and refer patients to other specialists or PCPs. Over half (59%) of respondents report that >40% of their patients are overweight or obese. Metabolic abnormalities lead respondents to stop or switch medications "sometimes" (61%), "often" (22%), or "very often" (2%).

Conclusions: Growing recognition of metabolic concerns surrounding bipolar disorder have prompted widespread monitoring of body weight and other metabolic parameters by psychiatrists. Abnormal findings require referrals for medical management, and stopping or switching bipolar therapies.

Session II - 19

Lamotrigine for Acute Treatment of Bipolar Depression: A Retrospective Pooled Analysis of Response Rates in 3 Randomized Trials

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Objective: Bipolar depression is a significant burden for patients and there is a need to improve methods used in clinical trials to identify effective treatments. A retrospective combined analysis of responder rates in three randomized, double-blind, placebo-controlled trials of lamotrigine for the acute treatment of bipolar depression is discussed.

Methods: Data were pooled from three randomized trials that included 579 participants with bipolar I or II disorder and who had a major depressive episode. Efficacy was evaluated weekly with the Montgomery-Asberg Depression Rating Scale (MADRS). The percentage of patients that achieved a ≥50% or a ≥75% improvement on the MADRS from baseline, and full remission of symptoms (MADRS ≤10 observed on 2 consecutive assessments) were compared between the lamotrigine and placebo groups by week. Since the studies were not equal in length, data were truncated to the shortest duration of the three studies (7 weeks).

Results: More patients treated with lamotrigine than placebo achieved a ≥50% improvement from baseline at weeks 5, 6, and 7 with 49% vs. 35% (p=0.003), 56% vs. 43% (p=0.007), and 64 % vs. 45% (p<0.001) responders, respectively. At week 7, more patients who received lamotrigine than placebo achieved a ≥75% or greater improvement from baseline (35% vs. 19% responders, p<0.001) and full remission of symptoms (38% vs. 27%, p=0.025).

Conclusions: Lamotrigine was superior to placebo in response and remission outcomes for the treatment of acute depression over 7 weeks in patients with bipolar disorder.

Session II - 20

Genetic Predictors of Response to Lithium in Bipolar Patients with Euphoric and Dysphoric Mania

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Lithium was the first mood stabilizer discovered and remains a mainstay of treatment of bipolar disorder. However, patients demonstrate highly individual patterns of response, making selection of optimal treatment challenging. This often results in a trial and error process of treatment, that can extend patient suffering. It has been argued that this individual variation has substantial genetic contribution. The goal of this study is to identify genes that predict response to lithium that may be of clinical utility. We have previously identified 92 lithium responders and 92 non-responders from a set of patients recruited for genetic studies of bipolar disorder. Lithium response was retrospectively assessed from a SCID or DIGS interview, a detailed lifechart and medical records. Response was judged by a panel of experienced clinicians blind to genotype. All episodes of treatment were considered for decrease in episode frequency or symptom severity in comparison to periods off lithium. Consistent with previous reports, several clinical variables correlated with response, including: euphoric mania, absence of rapid cycling, and absence of PTSD. In the first phase of this study, 88 variants were selected in 9 genes involved in lithium's mechanism of action or disease susceptibilty. SNPs in the NTRK2 gene were associated with response only in patients with euphoric mania; while a SNP in the GRK3 gene was associated with response only in patients with dysphoric mania. NTRK2 codes for the receptor for BDNF and provides further support for the role of this system in lithium response. Similarly, GRK3 is involved in receptor desensitization and implicates that system. This work is currently being extended in a second phase by examination of additional genes involved in proposed lithium mechanism of action. Our work suggests that a multi-gene predictor of lithium response may be developed by incorporating differences in clinical presentation.

Session II - 21

Mood and Suicidality in Patients with Frequently Relapsing Bipolar Disorder: Preliminary Data Supporting Adjunctive Therapy with Long-Acting Risperidone

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Background: A subset of patients with bipolar disorder (BD) relapse frequently, experiencing high levels of morbidity and poor outcomes. This trial evaluates the addition of long-acting risperidone (LAR) to treatment-as-usual on mood symptom control, functioning, and suicidality in patients with frequently relapsing bipolar disorder (FRBD).

Methods: Patients meeting criteria for BD and experiencing ≥4 episodes requiring clinical intervention in the past 12 months and 2 episodes in the past 6 months (n=84) received open-label (OL) augmentation of treatment-as-usual with LAR (25-50 mg) for 16 weeks. Remitters (Young Mania Rating Scale [YMRS] and Montgomery-Asberg Depression Rating Scale [MADRS] (10 over the last 4 weeks of OL) were eligible for randomization to placebo or LAR in a double-blind (DB), 52-week, relapse-prevention phase. Measures included MADRS, YMRS, and Clinical Global Impressions of Severity (CGI-S). Measures of suicidal thinking included the InterSePT Scale for Suicidal Thinking-Revised (ISST-R) and the MADRS–Item 10 (MADRS-10).

Results: At baseline, 64% of patients were moderately-markedly ill by CGI-S; 37% scored ≥20 on YMRS; 38% scored ≥20 on MADRS. Mean±SD YMRS and MADRS scores were 15.7±10.9 and 12.7±11.3, respectively. Seventy-four percent completed OL phase; 49% met remission criteria and eligibility to enter DB phase; 25% did not meet remission criteria but continued OL LAR treatment. Reasons for discontinuation from OL phase included adverse events (6%); loss to follow-up (1%); noncompliance (1%); protocol violation (1%); and withdrawal of consent (17%). At OL endpoint, patients with CGI-S scores of moderately ill or worse decreased to 19% (from 64%), and mean±SD YMRS and MADRS improvements were −10.4±11.3 (P<0.001) and −4.5±12.6 (P<0.05), respectively.

ISST-R data were available for 77 of the first 84 subjects enrolled. Mean±SD change was −0.4±1.9 (P<0.049). Of 20 subjects with suicidal thinking (ISST-R(1) at baseline), 16 decreased their ISST-R score (range, −9 to −1), 3 were unchanged, 1 increased. Mean±SD absolute and percentage changes among these 20 patients were −2.3±3.0 (P=0.003) and −69±66 (P<0.001), respectively. Of 57 patients without baseline suicidal thinking (ISST-R=0), 53 (93%) maintained ISST-R=0, and 4 (7%) showed increases in ISST-R scores (range, 2 to 3). Mean±SD change score for MADRS-10 in all subjects was −0.4±1.0 (P<0.002).

Conclusions: Preliminary OL findings suggest addition of long-acting risperidone to treatment-as-usual may reduce mood and suicidality symptoms in patients with FRBD. Long-term, double-blind, placebo-controlled data will indicate the validity of these early observations.

Session II - 22

Country Effects Among YMRS and HAMD Raters in Clinical Trials: Sources of Variability

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Background: The EMEA seeks documentation of inter-rater reliability prior to and during clinical trials. Training and assessing raters in multicenter CNS clinical trials aims to standardize administration and scoring of patient interviews, and minimize variance both between and within raters. However, in international trials, cultural norms, psychiatric training, or language issues may result in raters from different countries interpreting and rating the same behaviors differently.

Methods: The results of rater training programs performed in clinical trials of bipolar disorder. Raters from 11 countries watched and rated the same videotaped English YMRS interviews without subtitles; 4 countries were non-U.S. countries with English as the first language, 6 were non-U.S. countries without English as a first language but with a high level of English language competence, and the final country was the US. YMRS ratings were assessed with respect to Gold Standard (GS) ratings, devised by a panel of American experts, and countries with and without English as a first language were compared.

Results: Raters from 3 groups (the US, countries with English as a first language, countries without English as a first language) produced the same pattern of ratings across the individual YMRS items. YMRS raters from all 3 groups of countries scored very close to the GS on most items. For those items where there was some disagreement between the raters' scores on average and the GS, the direction of the disagreement held constant across the 3 groups. US raters scored closer, on average, to the GS total whereas raters from countries without English as a first language had the greatest deviation in their total YMRS scores from the GS total; raters from counties with English as a first language produced total YMRS scores which fell between the other two groups. Although there was an overall difference between the 3 groups of raters in terms of their total YMRS scores, the relative difference remained constant across virtually all of the YMRS items.
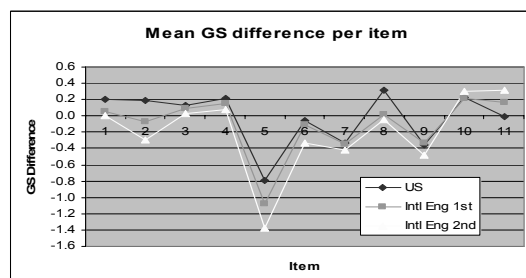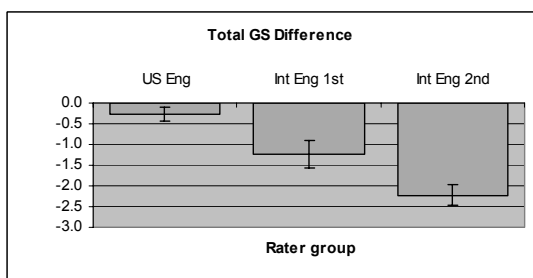
Conclusions: Despite potential cultural, psychiatric training, and language issues contributing to country differences, a rater training program can result in international raters who assess patients on these scales using similar standards, and obtain ratings close to ideal GS scores. For the YMRS, differences between the American panel GS and international ratings focus the issue of country effects in international trials on other factors, such as specific issues with the videotapes and instructions.

Session II - 23

An RCT of Flax Oil in Children and Adolescents with Bipolar Disorder

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Background: Deficient in Western diets, omega-3 fatty acids (O3FA) are essential plant-or marine-based lipids that may help stabilize mood. An appealing option for treatment in younger populations, they are likely to be well-tolerated, are cost-effective, and may be more acceptable as a "natural" substance. Flax oil was chosen due to lack of study in the bipolar population, frequent "over-the-counter" use as an alternative/complementary supplement, and greater acceptance by young patients who often refuse "fish oil."

Method: Forty-four children (ages 6-17 years) diagnosed with bipolar I or II disorder via K-SADS completed at least 2 weeks of a 16-week double-blind RCT, randomized to flax oil (550 mg alpha-linolenic acid/1,000 mg of flax oil) or placebo (olive oil) as monotherapy or adjunctive treatment. Dosing was titrated by 2,000 mg each visit as tolerated to 12,000 mg/day. Primary outcome measures were the Young Mania Rating Scale (YMRS), Child Depression Rating Scale-Revised (CDRS-R), and Clinical Global Impression (CGI-BP). Kaplan-Meier survival analyses compared length of time remaining in study across the two arms. Mixed effects models were run for primary outcome measures.

Results: Groups were equally balanced by age, race, sex, and lithium and antipsychotic use. No significant differences were found on primary outcome measures between the two groups. Those taking flax oil continued in the trial an average of 3 weeks longer (p=0.4). No differences occurred in rates of adverse events; one patient in each arm discontinued due to side effects. No subjects experienced worsening manic or hypomanic symptoms leading to study discontinuation; intractable mood issues pertained primarily to depression. One patient assigned to placebo made a suicidal gesture. Seven patients (14%) discontinued for mood issues, and 27 (53%) for any reason.

Conclusions: Flax oil does not appear useful for mood symptoms in children and adolescents with bipolar disorder, but may have physical health benefits. RCTs of omega-3 fatty acids can be completed and are well-tolerated in the pediatric population. Further study and recommendations for omega-3 fatty acid supplementation in bipolar disorder should focus on compounds containing fish-source docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA).

Session II - 24

Analyses of Treatment Efficacy in Subtypes of Adolescent Patients with Bipolar Disorder Treated with Olanzapine for Acute Mania: A 3-Week Randomized Double-Blind Placebo-Controlled Study

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Background: To date, there are limited data from large-scale controlled trials concerning the efficacy of treatments for bipolar disorder in adolescents. Furthermore, treatment efficacy in subtypes of adolescent patients with bipolar disorder has not previously been explored in detail. The objective of the present analyses was to examine the efficacy of olanzapine for the treatment of acute mania in subgroups of adolescent patients with bipolar disorder who presented with distinct illness characteristics (mixed, rapid cycling, psychotic features, early vs. late onset of bipolar disorder) and comorbid psychiatric conditions (ADHD, ODD).

Methods: In this 3-week, multicenter, randomized, double-blind, parallel trial, patients 13-17 years of age with a diagnosis of bipolar disorder manic or mixed received either olanzapine (2.5-20 mg/day; N=107) or placebo (N=54). Subgroups of adolescent patients with a current or lifetime diagnosis of ADHD or ODD, and those presenting with mixed, rapid cycling, psychotic features, and early onset of the disorder (onset age ≤12 yrs) were identified at the time of enrollment. The primary efficacy analysis was an analysis of covariance on mean change from baseline to endpoint in Young Mania Rating Scale (YMRS) total score. Additional efficacy analyses were performed on the Clinical Global Impression Scale (CGI-BP overall, mania, and depression severity), Children's Depression Rating Scale-Revised (CDRS-R), Overt Aggression Scale (OAS), and Attention Deficit/Hyperactivity Disorder Rating Scale (ADHDRS).

Results: Treatment with olanzapine was associated with significantly greater mean changes from baseline-to-endpoint in YMRS total score relative to placebo for patients with a mixed index episode (OLZ[n=61] -19.7, placebo[n=25] -10.0, p<.001), ADHD (OLZ[n=45] -19.5, placebo [n=13] -10.5, p=.003), ODD (OLZ[n=36] -17.9, placebo[n=12] -10.2, p=.028), and early onset age (OLZ[n=68] -16.0, placebo[n=29] -7.5], p<.001), but not for patients with psychotic features (OLZ[n=20] -7.7, placebo[n=7] -0.5, p=.11) or rapid cycling (OLZ[n=24] -13.7, placebo[n=5] -7.3, p=.27).

Conclusions: Treatment with olanzapine was effective in reducing the severity of mania symptoms in several subtypes of adolescent patients with bipolar mania.

Session II - 25

Effectiveness of Lamotrigine in a Clinical Setting

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Objective: To assess the effectiveness of lamotrigine in bipolar disorder (BD) patients in a clinical setting.

Methods: Open lamotrigine was naturalistically administered to BD outpatients assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation, and followed with the STEP-BD Clinical Monitoring Form.

Results: one hundred sixty-nine BD (55 type I, 98 type II, 16 NOS) patients (mean age 42.0±14.3 years, 64% female) taking a mean of 1.9 other psychotropic prescription medications received lamotrigine for a mean duration of 382±380 days, with a mean final dose of 236±144 mg/day. Only 44/169 (26%) patients discontinued lamotrigine; 12/169 (7%) for inefficacy, 6/169 (4%) for benign rash, 5/169 (3%) for nonadherence, and 21/169 (12%) for other reasons. Ninety-one of the 169 (54%) patients taking lamotrigine required subsequent additional pharmacotherapy; 39/169 (23%) for anxiety/insomnia, 28/169 (17%) for depressive symptoms; 19/169 (11%) for manic/hypomanic/mixed symptoms, and 5/169 (3%) for weight control. Mean time to addition of another psychotropic in these patients was 129±115 days. Thus, 54/169 (32%) continued lamotrigine with no subsequent psychotropic added (lamotrigine duration 271±347 days), 71/169 (42%) continued lamotrigine, but had subsequent psychotropic added (added subsequent psychotropic at 133±124 days, lamotrigine duration 562±414 days), and 44/169 (26%), discontinued lamotrigine (lamotrigine duration 227±208 days).

Conclusions: Lamotrigine had a low (26%) discontinuation rate and patients commonly did not require subsequent additional pharmacotherapy, suggesting effectiveness in a clinical setting.

Session II - 26

Retrospective Evaluation of Aripiprazole in Child and Adolescent Psychiatric Inpatients

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Background: Atypical antipsychotics have been used to treat aggression and other behavioral disorders in children and adolescents. To date, no randomized controlled trials using aripiprazole in children and adolescents have been conducted. Open label trials and retrospective chart reviews have shown promising results. Currently, none of the atypical antipsychotics is FDA approved for treatment of behavioral disorders in this population. The objective of this study was to retrospectively evaluate the effectiveness and tolerability of aripiprazole use in child and adolescent psychiatric inpatients.

Methods: This was a naturalistic, retrospective evaluation of patients treated with aripiprazole at the child and adolescent unit at the Austin State Hospital. Patient data collected from existing medical charts were evaluated for effectiveness and tolerability of aripiprazole using a chart extracted Clinical Global Impression of Improvement (CGI-I) and a chart extracted Clinical Global Impression of Severity of Illness (CGI-S) score. Demographic and clinical information was collected from patients' charts that met inclusion/exclusion criteria. To be included, patients had to be < 18 years of age and treated with aripiprazole for at least 2 consecutive weeks during their hospital stay.

Results: Forty-five patients met criteria and were included in this analysis. The mean age was 15.11 years ±1.46. Baseline and endpoint weights and heights were available for 22 patients. The mean weight change from baseline to endpoint was not significant t=0.658, df=21, $\sum$=7.131. Mean BMI change from baseline to endpoint was also not significant t=0.992, df=21, $\sum$=1.15.

Average CGI-S scores at baseline and endpoint were 5.11 ±0.91 and 3.33 ±1.24 respectively. This mean difference of -1.78 was statistically significant (t=8.748, df=44, $\sum$=1.363). Fifty-one percent of youth had a CGI-I score that was much improved or very much improved.

Aripiprazole was generally well tolerated; the most common adverse events reported were GI distress, n=8 (18%); nausea/vomiting, n=8 (18%); sedation, n=5 (11%); akathisia, n=4 (9%); headache, n=3 (7%); and EPS, n=2 (4%).

Conclusions: Improvement of CGI-S scores in these children and adolescents treated with aripiprazole for at least 2 weeks suggests a decline in symptom severity. Improvement was seen despite fairly severe baseline symptoms (mean CGI-S = 5.11) and a high prevalence of comorbid conditions. Aripiprazole was not associated with significant change in weight from baseline to endpoint and was generally well tolerated.

Session II - 27

The Aberrant Behavior Checklist: Use in Clinical Trials of Pediatric Autism

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Background: It is not known whether the Aberrant Behavior Checklist (ABC)[1] correlates with measures of core autism symptoms (Childhood Autism Rating Scale [CARS]) and changes in global clinical condition.

Methods: We evaluated a subpopulation of children (5–12 years) with autism and a baseline CARS score =30 (n=55) enrolled in an 8-week, randomized, double-blind, placebo-controlled trial of risperidone (0.01–0.06 mg/kg/day) for pervasive developmental disorders.[2] Pearson's correlations between ABC total and each of the five subscale scores and CARS subscale scores, and the Clinical Global Impressions–Severity (CGI-S) at baseline, or the CGI-Change (CGI-C) score at all visits were calculated.

Results: At baseline, six of the 15 CARS subscales (II-imitation, IV-body use, V-object use, VI-adaptation to change, XI-verbal communication, XIII-activity level) showed a significant positive correlation with one or more of the ABC subscales, with the strongest correlation observed for ABC-stereotypic behavior and CARS-imitation (r=0.444; P=0.001; n=53). ABC total scores showed a positive correlation with CARS subscales II, V, XIII (P<0.05 for each). At baseline, there were no significant positive correlations between the CGI-S and ABC scores total or subscale scores.

At all consecutive visits, there was a significant correlation between ABC total scores and CGI-C scores, which increased to r=0.555 at endpoint (P<0.0001; n=53). Few significant correlations were observed between CARS baseline scores and ABC subscale scores over time.

Conclusions: In this population, baseline severity of six CARS symptoms correlated to baseline ABC subscales. ABC scores correlated well with change in global condition during the trial, indicating that the ABC score is sensitive to pharmacological treatment effects in children with autism. However, few significant correlations were observed between changes over time on ABC subscales and CARS baseline scores, which suggests the ABC may be sensitive to treatment effects irrespective of the baseline severity of autistic symptoms.

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Session II - 28

CHQ and CGAS in an Open-Label Study of Ziprasidone in Pediatric Patients with Bipolar Disorder, Schizophrenia, or Schizoaffective Disorder

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Background: Impairment in functioning is common in pediatric patients with mood and psychotic disorders. A ziprasidone trial included exploratory measures to better understand the nature of these deficits.

Methods: Subjects were randomized to two open-label monotherapy dosing regimens. Ziprasidone was titrated over 7 to 10 days from 10-40 mg BID (Group 1) or from 20-80 mg BID (Group 2) followed by treatment at fixed doses for up to 3 weeks. Subjects could continue flexible-dose treatment for 6 months, with concomitant therapy permitted. Inclusion criteria included ages 10 to 17 years; bipolar I disorder (YMRS score (17); or schizophrenia/schizoaffective disorder (BPRS score >35 and >4 on at least one of unusual thought content, hallucinations, suspiciousness, or conceptual disorganization). Efficacy measures were YMRS, BPRS-A, CGI-S, and CGI-I. Exploratory measures were CHQ (Baseline) and CGAS (Baseline, Day 4, Weeks 1-4, 12, and 27).

Results: Twenty-three and 40 subjects were enrolled into Groups 1 (15 bipolar, 8 schizophrenic/schizoaffective) and 2 (31 bipolar, 9 schizophrenic/schizoaffective), respectively. At baseline, all subjects scored below norms for their age on the CHQ Global Psychosocial Health Score. In contrast, few subjects demonstrated impairment on CHQ Global Physical Health Score. Other CHQ subscales showed a similar pattern. Baseline means (SD) on CGAS were 41.74 (9.87) for Group 1 and 38.98 (10.00) for Group 2. Mean changes from baseline to Week 3 were 14.41 (13.65) and 17.41 (15.44) for Groups 1 and 2, respectively. About two-thirds of the improvement was observed by Week 1. An exploratory mixed-model analysis confirmed rapid initial improvement, which was maintained up to 6 months. No subjects at baseline, and five subjects at Week 3, scored > 70, the cutoff for normal functioning on CGAS. CGAS changes modestly correlated with the clinically relevant improvement on efficacy measures.

Conclusions: Bipolar subjects had baseline impairments in functioning similar to schizophrenia/schizoaffective subjects. Little impairment on physical health was observed. With ziprasidone treatment, clinically meaningful improvement in functioning paralleled that observed for the efficacy measures, and was observed as early as the first week. The CHQ and CGAS are useful supplements to efficacy measures in clinical trials.

Session II - 29

A Review of Antidepressant Prescribing Practices in a Large, National, Managed Care Database of Pediatric Patients Prior to and After Black-Box Warnings

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Background: After a thorough safety review, the FDA issued a black-box warning in October 2004 to alert prescribers of the potential for an increased risk for suicidality with the use of antidepressants in the pediatric population. While not intended to discourage appropriate prescribing, concerns have arisen that the warning would result in a hesitancy to use these potentially effective pharmacologic treatments. We examined healthcare claims data from a large U.S. health plan before and after the black-box warnings were issued to determine their impact on antidepressant prescribing trends in the pediatric patient population.

Methods: Using de-identified data, we examined antidepressant prescribing trends one year before and one year after the black-box warnings were issued (November 2003 to October 2004 for "baseline" and November 2004 to October 2005 "post-warning"). Eligibility criteria included patients of any gender, aged 0 to 17 years, receiving a prescription claim for an antidepressant during the analysis periods. The data were limited to outpatient retail, mail order, and specialty pharmacy claims. Antidepressant products were identified at the National Drug Code (NDC) level. Additionally, we examined changes in prescribing practices for specific medications as well as commonly associated diagnoses and comorbidities.

Results: The number of eligible patients included in the database in each time period was roughly 3.8 million. Of these, 62,371 were patients aged 0-17 taking an antidepressant at baseline, mainly for a major depressive disorder. Post-warning, 56,258 met eligibility criteria. About half were aged 15 to 17, with a similar distribution of males and females overall. The number of patients receiving an antidepressant decreased 9.8% post-warning; the number of patients receiving an SSRI or SNRI specifically decreased 11.9%. The greatest percentage decrease (14.5%) occurred in patients aged 5 to 9 years. Prescriptions for sertraline and venlafaxine decreased 14.9% and 29.6%, respectively, post-warning. Conversely, fluoxetine and bupropion prescriptions increased 17.8% and 15.1% respectively.

Conclusions: In general, it appears that the black-box warning is associated with a decrease in utilization of antidepressants in the pediatric population. Further evaluation is required to assess the impact of the decrease in antidepressant prescribing.

Session II - 30

Callous Unemotional Traits: A New Target for Pharmocotherapy

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Background: Aggressive and antisocial behaviors are the leading cause of all child and adolescent referrals to mental health clinicians, yet we have few effective pharmacological agents available to treat these conditions. In part this may be due to the heterogeneous nature of aggressive behavior and the probable diversity of contributing causes to its development and expression. Recently, new evidence has emerged showing that callous-unemotional (CU) traits among aggressive children and youth may be heritable. While there have been studies of the heritability of aggressive behavior and considerable evidence for the role of serotonin neurotransmission in its etiology, few studies have focused on specific gene systems and none have examined specific genes among children and youth with CU traits. Advances in genetics raise the hope that certain polymorphisms will be identified for which pharmacological preparations can be designed to target specific biochemical pathways believed to play a role in the expression of behavioral symptoms. The present study is the first to investigate the relation between CU traits and polymorphisms in the serotonin transporter gene (5-HTT) in aggressive children.

Methods: Fifty clinically referred male Caucasian children [Age = 9.4 ± 2.6 years] participated in this study. Inclusion criteria consisted of scores at or exceeding the 90th percentile on the Aggression subscales of both the Child Behaviour Checklist (CBCL) and the Teacher's Report Form (TRF) and a minimum 2-year history of aggression. Written informed consent was obtained from all participants. Participants were genotyped for polymorphisms in the variable number of tandem repeats in intron 2 (VNTR-2) and a 44-bp insertion/deletion in the promoter region (5HTTLPR) of the 5HTT gene. CU traits were assessed via parental ratings on the Psychopathy Screening Device (PSD).

Results: A significant association was found between the VNTR-2 polymorphism and the CU subscale on the PSD (ANOVA, $p=0.011$). Specifically, individuals with the 12R allele, especially those with 12/12 genotypes, had higher CU scores. No association was found for the 5HTTLPR polymorphism.

Conclusions: A genetic association between callous-unemotional traits and aggression could help identify a unique subgroup of aggressive children who may require more focused intervention strategies. Though preliminary, this finding holds out hope that a specific genetic marker could become the focus for the development of new drugs designed to target the protein products of this polymorphism.

Source of Funding: Centre for Addiction and Mental Health Foundation

Session II - 31

Longitudinal Patterns of Multiple Psychotropic Use Among Children and Adolescents

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Background: Multiple psychotropic medication use for children and adolescents has increased. It is more common among males, older youths, and those seen in psychiatry specialty practices. Because research on multiple psychotropic use among children and adolescents treated in outpatient settings has been limited to cross-sectional studies, this study examined the continuity of treatment and medication switching over time.

Methods: A two-year, longitudinal study of multiple psychotropic treatment was conducted using Medicaid claims data. The cohort was identified from the population of individuals less than 20 years old who were continuously enrolled in a Mid-Atlantic state Medicaid program, received two or more different psychotropic classes in 1998, and received mental health treatment in 1998 and 1999 (N=1,032). Psychotropic utilization was examined to distinguish multiple use, defined as simultaneous treatment with two or more different classes in the same month, from medication switching, where use of different psychotropic classes did not overlap in the same month. The cohort was stratified by psychotropic use in January 1998 as no multiple use and two or more psychotropic classes.

Results: The cohort was primarily male (69%), aged 5-14 years old (75%), and white (62%). Nearly half (47%) had attention deficit/hyperactivity disorder, 16% had depression, and 15% had conduct disorder. Two-thirds were seen by a mental health provider. Of the 775 with no multiple use in January 1998, 16% never received multiple medications, 35% switched to multiple use only once, and 49% switched on and off of multiple psychotropic classes several times during 1998. Of the 257 receiving two or more psychotropic classes in January 1998, 3% continued on this regimen, 12% switched once, and 85% switched on and off multiple medications several times. Among these 257 children and adolescents, 49% also received two or more psychotropic medications in January 1999.

Conclusions: Less than 5% received multiple psychotropic classes continuously without switching in 1998. The majority experienced several changes over a two-year period. It is necessary to further understand how these utilization patterns relate to clinical severity and therapeutic outcomes.

Session II - 32

Tolerability of OROS® MPH for Treatment of ADHD Plus Epilepsy

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Background: The prevalence of attention deficit/hyperactivity disorder (ADHD) in children with epilepsy is between 12-39%[1]; however, there are no studies for this population on the utility of OROS®-methylphenidate (MPH). Two short term prospective studies have found immediate release methylphenidate safe in children with well controlled seizures.[2,3] Longer term-observational studies have reported conflicting findings.[4,5]

Methods: Twenty-seven patients (10.7±3.1 years) on antiepileptic drugs, 1-month seizure free, were randomized to OROS-MPH or placebo and crossed-over double-blind. Each dose (18, 36, 54 mg) was tested for 1 week. Clinical Global Impressions (CGI)-Improvement scale scores, adverse events (AEs), and seizures were evaluated. Response was defined as a CGI-Improvement score of "much" or "very much" improved.

Results: There were no serious AEs. The weekly rate of seizures at baseline (0.03±0.05) did not increase (0.01±0.04). Seizures occurred during both active treatment and placebo in two patients, and during placebo treatment only in one other patient. Higher mg/kg doses predicted response (P<0.001). The titration schedule called for only patients who tolerated lower doses to be exposed to higher ones. Thus, 27 patients received 18 mg (0 discontinued, 11 responded to OROS-MPH, 2 responded to placebo). Twenty-four patients received 36 mg (8 discontinued OROS-MPH, 0 discontinued placebo, 13 responded to OROS-MPH, 3 responded to placebo). Twelve subjects received 54 mg OROS-MPH, and 16 subjects received 54 mg placebo (2 discontinued on OROS-MPH, 4 discontinued on placebo, 9 responded to active, 1 responded to placebo).

Conclusions: OROS-MPH produced significant response rates in ADHD symptoms compared with placebo, with no increase in seizures or serious AEs in children with ADHD plus epilepsy.

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Session II - 33

An Open-Label Trial of Escitalopram for Prophylaxis of Major Depression in Hepatits C Before and During Combination Therapy with Pegulated Interferon and Ribavirin

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Background: Depression is common among patients with hepatitis C and can be induced by interferon alpha, used to treat this viral illness. Depression is a major reason for discontinuing interferon therapy, leaving such patients at increased risk for possible adverse outcomes, including cirrhosis and liver failure. Management of depression is important for the mental and physical health of these patients. This study aimed to determine whether patients with a history of major depression could complete a course of peginterferon alpha-2a and ribavirin for hepatitis C, if first treated with escitalopram, and to estimate the relapse rate of depression during a course of therapy with peginterferon alpha-2a and ribavirin in subjects pre-treated with escitalopram.

Methods: Ten patients with a history of major depressive disorder, in remission, were treated with escitalopram with the intent of preventing the recurrence of major depression during treatment with peginterferon and ribavirin. Escitalopram 10mg daily was initiated 4 weeks prior to, and continued throughout the course of, interferon therapy, either 24 or 48 weeks, depending on hepatitis C genotype. Dosage adjustments were made as needed. The Hamilton Depression Rating Scale (Ham-D), the Medical Outcomes Short Form, and the Hopkins Symptom Checklist-90 were administered, along with other measures at pre-baseline, baseline, and 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 weeks.

Results: Throughout the course of treatment, there were no statistically significant increases in mean Ham-D scores, compared to baseline. The mean Ham-D score prior to initiation of any treatment was 3.90 (95% CI 2.17-5.63, p=0.3874). The highest mean score during treatment was 8.22 (95% CI 4.33-12.12, p=0.568), observed at week 16. Nine of the 10 subjects (90%) completed their course of interferon alpha and ribavirin therapy without significant psychiatric complications. One subject was terminated following substance abuse relapse at week 14. Relapse of major depression was defined as a Ham-D score of 15 or greater. Two subjects had pathologic Ham-D scores of 15 and 17 at weeks 12 and 24, respectively. One of these subjects was the subject who was terminated for substance abuse relapse. Eight of 10 subjects maintained Ham-D scores of <15 throughout the entire study. Mean escitalopram dosage at endpoint was 15.5mg daily.

Conclusions: Pre-treatment with escitalopram in subjects with major depressive disorder, in remission, may allow for completion of a course of interferon and ribavirin therapy for hepatitis C, without significant recurrence of symptoms of major depression.

Session II - 34

A Randomized, Double-Blind, Placebo-Controlled Trial of Sodium Oxybate in Fibromyalgia Syndrome (FMS)

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Background: There is no FDA-approved medication for treating fibromyalgia syndrome (FMS). Sodium oxybate (Xyrem®) is currently approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. We conducted a proof-of-principle study to examine the efficacy and safety of oxybate in FMS.

Methods: One hundred ninety-five patients with primary FMS were randomized to receive oxybate (4.5 g or 6 g per day) or placebo for 8 weeks. The primary outcome variable (POV) was a composite of changes from baseline in three co-primary, self-report measures: Pain Visual Analog Scale (PVAS), Fibromyalgia Impact Questionnaire (FIQ); and Patient Global Assessment (PGA). Secondary outcome measures included changes in sleep quality (SLP), and the Total Tender Point Count, (TTP). Intent-to-treat (ITT) analyses to examine changes from baseline and a post-hoc correlation analysis between the PVAS and SLP were performed.

Results: The ITT population included 188 patients (placebo, n=64; oxybate 4.5g, n=58; oxybate 6g, n=66), of whom 147 (78%) completed the trial. Significant benefit in the POV was seen with both doses of oxybate compared with placebo (4.5g, p=0.005). SLP was improved with both dosages of oxybate (4.5g, p=0.004). The TTP was significantly improved only with the 6g dose (p = 0.05). A significant correlation was seen between change in PVAS and change in SLP (r=0.55, p<0.001). Oxybate was well tolerated, as illustrated by the high rate of study completion. As expected, dose-related nausea and dizziness were observed more with oxybate but there were no unexpected adverse events.

Conclusion: Oxybate therapy of FMS was safe and significantly improved the major symptoms of FMS (pain, tenderness, insomnia). Improved sleep quality appears to contribute to the reduction in pain. Sodium oxybate represents a novel therapeutic option for FMS and warrants further study.

Session II - 35

The Effects of Comorbid Anxiety Symptoms on the Effectiveness of Pregabalin in Treating Central Neuropathic Pain Associated with Spinal Cord Injury

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Background: Patients with spinal cord injury (SCI) commonly have comorbid anxiety disorders. Pregabalin is approved in the United States for the treatment of pain associated with diabetic peripheral neuropathy and postherpetic neuralgia, and it has shown rapid, sustained efficacy for treating pain associated with SCI. Pregabalin also has demonstrated significant efficacy for treating generalized anxiety disorder in six of seven randomized, controlled trials. We sought to determine whether the presence of clinically meaningful anxiety symptoms at baseline, identified by using the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) score, influenced pregabalin's efficacy for treating central neuropathic pain associated with SCI.

Methods: One hundred thirty-seven SCI patients were randomized to flexibly dosed pregabalin (150-600 mg/d) or placebo for 12 weeks. Pain relief was assessed by mean change from baseline to endpoint in pain score (based on an 11-point scale derived from patients' daily pain diaries). The HADS was administered at baseline and endpoint. For this analysis, patients were stratified into two groups: baseline HADS-A score less than or equal to 10 (indicating no or mild anxiety symptoms) and baseline HADS-A score >10 (indicating moderate to severe anxiety symptoms).

Results: Pregabalin-treated patients received a mean daily dosage of 388 mg. Fifty-eight pregabalin-treated patients and 47 of those who received placebo had a baseline HADS-A score less than or equal to 10, while 11 pregabalin-treated patients and 20 of those who received placebo had a baseline HADS-A score >10. Regardless of HADS-A stratum, patients treated with pregabalin had significantly greater reduction in pain score from baseline to endpoint than did those receiving placebo: HADS-A less than or equal to 10, -1.69 vs -0.58, P=.001; HADS-A >10, -4.12 vs 0.41, P<.001. Pregabalin treatment was also associated with significant reduction in HADS-A score from baseline to endpoint relative to placebo (-1.72 vs -0.66, P<.05).

Conclusions: Pregabalin efficaciously treated pain in patients with and without comorbid anxiety symptoms. In addition, treatment with pregabalin was associated with a statistically significant decrease in HADS-A subscale score from baseline to endpoint, suggesting improvement of comorbid anxiety.

Session II - 36

Early Onset of SSRI Antidepressant Action: Systematic Review and Meta-Analysis

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Background: Selective serotonin reuptake inhibitors (SSRIs) are often described as having a delayed onset of effect in the treatment of depression. However, some trials have reported clinical improvement as early as the first week of treatment. We tested the alternative hypotheses of delayed or early onset of antidepressant action with SSRIs.

Methods: Randomised controlled trials of SSRI versus placebo for the treatment of unipolar depression in adults that reported outcomes for at least two time points in the first 4 weeks of treatment (38 studies included from >500 citations identified) were included.

Results: Pooled estimates of treatment effect on depressive symptom rating scales were calculated for weeks 1 to 6 of treatment. In the primary analysis, the pattern of response seen was tested against alternative models of onset of response.

The primary analysis incorporated data from 28 randomised controlled trials (n=5872). A model of early treatment response best fit the experimental data. Treatment with SSRI rather than placebo was associated with clinical improvement by the end of the first week of use. A secondary analysis indicated an increased chance of achieving a 50% reduction in Hamilton Depression Rating Scale score by week 1 (relative risk 1.64, 95% Confidence Interval 1.2 to 2.25) with SSRI treatment, compared to placebo.

Conclusions: Treatment with SSRIs is associated with symptomatic improvement in depression by the end of the first week of use, and continues to accumulate at a decreasing rate for at least 6 weeks.

Source of Funding: None

Session II - 37

The Treated Incidence, Identified Prevalence, and Surveillance for Diabetes Mellitus Among Inpatients in State-Operated Psychiatric Hospitals in New York State, 1997-2004

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Objectives: To describe the incidence of newly treated diabetes mellitus, prevalence of identified cases of diabetes mellitus, and surveillance for new cases of diabetes mellitus over the period 1997 to 2004 among inpatients in a large state psychiatric hospital system.

Methods: Prevalence of diabetes mellitus was determined by ascertaining the number of individuals receiving antidiabetic medication and/or having a diagnosis of diabetes mellitus for each calendar year, using a database containing diagnostic and drug prescription information from the in-patient facilities operated by the New York State Office of Mental Health. Yearly incidence was calculated by identifying unique patients who received new prescriptions of antidiabetic medication among patients with no known prior history of receiving an antidiabetic medication or having a recorded diagnosis of diabetes mellitus. Data were categorized by calendar year, gender, age, race/ethnicity, and psychiatric diagnosis, and relative risk ratios were calculated. Surveillance for abnormal plasma glucose levels was measured by calculating the number of plasma glucose tests completed per 100 patient-days among patients without diabetes mellitus.

Results: Prevalence of identified cases of diabetes mellitus increased from 6.9% of 10,091 patients in 1997 to 14.5% of 7,420 patients in 2004 (risk ratio comparing 2004 to 1997 2.11, 95% confidence interval 1.93-2.31). The incidence of newly treated diabetes mellitus increased from 0.9% in 1997 to 1.8% in 2004 (risk ratio of 2.03 [1.51-2.73]). The increase in incidence of newly treated cases and prevalence of identified diabetes was only partially explained by the increase in surveillance for new cases, which increased from 1.23 plasma glucose tests per 100 patient-days in 1997 to 1.80 in 2002 (risk ratio of 1.46 [1.43-1.50]).

Conclusions: The doubling of the treated incidence rate and the rise in prevalence of identified cases of diabetes mellitus among psychiatric inpatients mirrors the rise observed in the general population, but with higher absolute rates.

Source of Funding: None

Session II - 38

Cardiovascular and Metabolic Health Status in Schizophrenia Patients Screening for Clinical Trial Participation

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Background: Patients with schizophrenia are at greatest risk for the development of co-morbid metabolic and cardiovascular illness. In particular, use of antipsychotic medications has been implicated as a contributing factor.

Methods: We investigated metabolic and cardiovascular status, including fasting blood sugars (FBS), fasting lipids, body mass index (BMI), blood pressure and electrocardiography (ECG), in 305 chronically ill (39.1 ± 9.7 years old; 18.1 ± 9.7 years ill) patients with schizophrenia (211 M, 77.2% African-American) who were on typical and atypical antipsychotics. Patients had no previously diagnosed cardiovascular or metabolic illness, and were screening for participation in clinical drug trials.

Results: 87.5% of patients were treated with atypical antipsychotics, either monotherapy or in combination (7.5% on aripiprazole, 36.8% on olanzapine, 30.7% on risperidone, 23.9% on quetiapine, and 6.8% on ziprasidone) versus 12.5% on typical antipsychotics alone. In 276 patients with BMI measurements, 72% were overweight (BMI> 25 kg/m2) with 44% in the obese range (BMI>30 kg/m2). In 293 patients with fasting lipids, cholesterol and triglyceride levels were elevated in 43% and 30% of patients, respectively. Caucasian patients had statistically higher triglyceride levels than did African American or Hispanic patients (t=-2.741, p<.05). In 284 patients with fasting blood sugars, glucoregulatory impairment was found in 18% of patients, with 9% having frank diabetes (FBS$\geq$126 mg/dL). Of 305 total patients, 14% were hypertensive (diastolic BP $\geq$ 85 mmHg) and 53% had abnormal ECGs, including 74 patients with evidence of ischemic heart disease. No statistically significant associations of any of these parameters were found among different atypical antipsychotics or between typical and atypical antipsychotic treatment.

Conclusion: High rates of obesity, hypertriglyceredemia, hypercholesterolemia and ECG abnormalities in our patients underscore the need for increased screening in schizophrenia patients for co-morbid medical conditions, which are often under-recognized in this population. Although most of our patients were treated with atypical antipsychotics, lack of association among various atypical and typical agents, alone and in combination, suggests other contributing factors, eg. ethnicity. Further data regarding metabolic and cardiovascular abnormalities will be presented in an expanded patient sample.

Session II - 39

The APOE E4 Allele Influences Delayed Recall of Pre-Drug Primacy Words After Placebo and Acute Lorazepam Administration in Healthy Elderly

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Background: Primacy and recency effects are well-known aspects of memory in which immediate recall of unrelated items from the beginning and end of a list is better than that for items in the middle. However, the primacy effect is markedly reduced or absent in Alzheimer's disease (AD), and deficits have also been reported in healthy adults with the APOE-e4 allele, a major risk factor for AD. Interestingly, acute oral administration of alcohol and benzodiazepines such as lorazepam, which produce sedative and profound anterograde amnestic effects, enhances delayed recall of pre-drug primacy words. This well-recognized phenomenon is known as retrograde facilitation (RF) and has been ascribed to decreased retrograde interference from the anterograde amnestic effects. We previously reported that in high–functioning healthy elderly, the APOE e4 allele was associated with decreased recovery from the amnestic effects resulting from acute oral lorazepam doses. Thus we tested the hypothesis that the APOE e4 allele would be associated with enhanced lorazepam-induced RF of pre-drug primacy words.

Methods: Sixty-four cognitively intact, healthy elderly (mean age, 66.1 years) participated in three testing sessions, one week apart, during which they were administered a single oral dose of placebo or lorazepam (0.5 mg or 1.0 mg). Psychometric tests, including immediate and delayed recall of equivalent 16-word lists, were administered at baseline and at 1, 2.5, and 5 hours following acute drug or placebo administration. Primacy and recency positions from the pre-drug word list were defined according to previously published methods.

Results: RMANOVAs, with e-4 allele (yes vs. no) as a between-subjects factor, revealed a significant drug X position X e-4 group interaction. In the 1.0 mg lorazepam condition, participants with the e4 allele remembered significantly more words from the initial positions on the list (primacy) relative to participants without the e4 allele. In the placebo condition, subjects with the e4 allele recalled significantly fewer words from the first half of the pre-drug word list than the second half, whereas the opposite was observed in those without the allele.

Conclusions: Compared to elderly subjects without an APOE e4 allele, subjects with the APOE e4 allele who were cognitively intact by traditional tests showed reduced recall of primacy words in the placebo condition, but better recall of primacy words after acute lorazepam administration, thereby enhancing their RF effect. These findings suggest that one of the effects of the APOE e4 allele on memory may be an increased susceptibility to retrograde interference. Abnormal primacy effects may be the earliest manifestation of APOE e4 in learning and memory.

Session II - 40

Effect of Memantine on Behavioral Outcomes in Moderate to Severe Alzheimer's Disease

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Background: Memantine is a moderate affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist approved in the United States and Europe for the treatment of moderate to severe Alzheimer's disease (AD). Memantine blocks prolonged pathological activation of NMDA receptors, which may play a role in the pathogenesis of AD, while allowing normal receptor function during conditions of learning and memory. In this 24-week double-blind, placebo-controlled trial, behavioral symptoms were monitored in moderate to severe AD patients (N=404) receiving memantine or placebo in addition to stable donepezil treatment. The primary analysis of this study previously demonstrated significant benefits of memantine on functional, cognitive, and global measures at study endpoint.

Methods: In this study, post hoc analyses of behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI), administered at baseline, Week 12, and Week 24. The statistical analysis (ANCOVA) was based on the ITT population using an LOCF approach.

Results: Baseline characteristics between the placebo and memantine groups were comparable. At Week 24, there was a statistically significant reduction in behavioral disturbances and psychiatric symptoms in memantine-treated patients compared to placebo-treated patients (P=.002). In addition, several NPI domains demonstrated statistically significant treatment differences in favor of memantine at Week 24. These domains were agitation/aggression (P=.001), irritability/lability (P=.005), and appetite/eating change (P=.045). When patients asymptomatic at baseline were examined, significantly fewer memantine patients exhibited emergence of delusions (P=.011) and agitation/aggression (P=.032) at Week 12 and agitation/aggression (P=.016), irritability/lability (P=.041), and nighttime behavioral disturbances (P=.027) at Week 24 compared to placebo patients. When patients symptomatic at baseline were examined, there was significantly less worsening compared to placebo in symptoms of agitation/aggression (P=.018, Week 12; P=.021, Week 24) and appetite/eating changes (P=.012, Week 12).

Conclusions: As behavioral symptoms affect the quality of life of both patients and caregivers, the effective treatment of such behaviors represents a significant goal of patient therapy. In addition, the potential for memantine to reduce the need for concomitant antipsychotic medications merits further investigation.

Session II - 41

A Comparison of Bupropion XL with Venlafaxine XR for the Treatment of MDD: An Evaluation of the Relative Effects on Sexual Functioning, Efficacy, Safety, and Tolerability

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Background: Bupropion has consistently demonstrated comparable antidepressant efficacy and improved tolerability (less sexual dysfunction and sedation) in direct comparisons with SSRIs. Limited data suggest that the incidence of sexual dysfunction with venlafaxine is similar to treatment with SSRIs and significantly greater than with bupropion. However, large well-controlled clinical trials and direct head-to-head comparisons between once-daily bupropion XL and venlafaxine XR were lacking.

Methods: This 12-week, randomized, double-blind, multi-center trial compared bupropion XL (150-450 mg/day) and venlafaxine XR (75-225 mg/day) in 342 adult outpatients with moderate-severe MDD with respect to sexual functioning, efficacy, and safety. Overall sexual functioning was evaluated using the Changes in Sexual Functioning Questionnaire (CSFQ-C). Efficacy measures included the HAMD-17, CGI-S, and CGI-I. The Frequency and Intensity of Side Effect Rating (FISER) and Global Rating of Side Effect Burden (GRSEB) scales were used in addition to routine safety evaluations at clinic visits.

Results: Whereas sexual functioning improved in MDD patients treated with bupropion XL, it worsened in patients treated with venlafaxine XR. The differences were statistically significant at each time point beginning with Week 2 ($p = 0.006$) and across weeks 5, 6, 9, and 12 simultaneously ($p = 0.005$). Among the subgroup of patients with normal sexual functioning at baseline (77%), sexual functioning remained stable in the bupropion XL group, while it significantly worsened in the venlafaxine XR group ($p < 0.05$ relative to baseline). Patients' depression improved comparably when treated with either bupropion XL or venlafaxine XR as measured by mean changes from baseline in HAMD-17 total score (-13.7 vs. -12.8, respectively, 95% CI [-2.66, 0,87]) and CGI-S (-1.9 vs. -1.8, 95% CI [-0.35, 0.15]); however, the remission rates (HAMD-17 = 7 at Week 12) favored bupropion XL: 46% vs. 33%, 95% CI (1.07, 3.46).

Conclusions: Sexual functioning worsened in depressed patients treated with venlafaxine XR relative to patients treated with bupropion XL. Comparable improvements in efficacy were observed with both treatments as measured by HAMD-17 and CGI-S, although remission rates and side effect burden also favored bupropion XL.

Session II - 42

Antidepressant and Anxiolytic-Like Effects of Novel Neuronal Nicotinic Acetylcholine Receptor Ligands

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Abstract: Increasingly, clinical and experimental data support a potential therapeutic benefit of targeting nicotinic acetylcholine receptors (nAChRs) in depressive and anxiety disorders. Previously, we reported on a novel nAChR-selective ligand, TC-1707, that displayed antagonistic actions at the alpha4beta2 nAChR subtype and was much more potent than fluoxetine in reversing immobility in the forced swim test (FST). While TC-1707 exhibited the potential to treat depression, its continued development as a drug candidate was compromised due to its poor metabolism profile. The present studies report on a novel alpha4beta2 nAChR-selective ligand that exhibits antagonistic-like actions with an improved pharmacokinetic profile. TC-2216 was assessed in animal models commonly used to evaluate potential antidepressants (FST and behavioral despair) and anxiolytics (social interaction, light/dark test, and elevated plus maze). TC-2216 is potent in reducing immobility in the mouse behavioral despair and in the rat FST, and is more potent than classic antidepressants (i.e., desipramine and imipramine). Furthermore, the effects of TC-2216 on immobility are dissociated from its effects on locomotor activity. TC-2216 is equipotent to nicotine in reducing social anxiety in the social interaction test and in increasing time spent in a mildly aversive environment (i.e., light) as assessed by the light/dark test. TC-2216 exhibits anxiolytic-like activity in the one-trial elevated plus maze following acute administration. Additional information suggests that TC-2216 might possess anti-obesity properties. TC-2216 is well tolerated in vitro and in vivo and is negative in mutagenicity bioassays. Currently, TC-2216 is being assessed in preclinical toxicology studies. Taken together, these findings suggest that TC-2216 may represent a novel class of therapeutic antidepressant/anxiolytic agents.

Session II - 43

Predicting Remission in Depressed Outpatients Treated with Venlafaxine Extended Release (XR) or Selective Serotonin Reuptake Inhibitors: Analysis of Symptom - Improvement Patterns

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Background: This subanalysis of a 180-day, rater-blinded, open-label study in depressed outpatients was designed to examine the patterns of symptom improvement in the first 4 weeks of treatment and how these patterns relate to remission with venlafaxine XR (extended release) or selective serotonin reuptake inhibitors (SSRIs).

Methods: Outpatients (n=1385) with major depressive disorder (MDD) and a total score ≥ 20 on the 17-item Hamilton Depression Rating Scale (HAM-D$_{17}$) were randomly assigned to receive venlafaxine XR 75–225mg/day (n=688) or an SSRI (n=697): fluoxetine 20–80mg/day, paroxetine 20–50mg/day, citalopram 20–40mg/day, and sertraline 50–200mg/day. Remission rates for venlafaxine XR and SSRIs were compared at 90 days. Remission was defined as a HAM-D$_{17}$ total score ≤ 7. The three symptom domains evaluated were mood, psychic anxiety, and somatic symptoms. A fourth domain, combining the anxiety and somatic symptoms was also evaluated. Patient change scores on the above symptom domains during the baseline to day 14, day 14 to 30, and baseline to day 30 treatment periods were compared with remission status at day 90.

Results: Ninety-day remission rates were 35.0% (193/552) and 29.5% (163/553) for venlafaxine XR and SSRIs, respectively; this difference was not statistically significant. The predictors that best distinguish between remitters and non-remitters (at day 90) for venlafaxine XR treated patients are the day 14 to 30 mood (P=0.0006) and somatic symptom (P=0.0005) domain change scores, while the day 14 to 30 somatic (P=0.0052) domain change score was the best predictor for the SSRIs. For both treatment groups, baseline to day 30 mood and somatic domain change scores were also significant predictors of 90-day remission (P<0.0001).

Conclusions: The results of this open-label trial suggest that early symptom improvement patterns may aid in predicting remission to antidepressant treatment. Furthermore, agents impacting different neurotransmitter systems may differ slightly in their symptom improvement patterns, even when final symptom improvement levels are comparable.

Session II - 44

Use of Selegiline Transdermal System (STS) in Patients with Recurrent Depressive Episodes

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Background: Patients who experience a depressive episode are likely to suffer from future episodes.[1,2] In fact, research has demonstrated that up to 80% of all depressed patients experience a relapse at some time during their lifetime.[3,4] Recurrent depressive episodes substantially contribute to the overall burden of illness.[5] The objective of this study was to determine the efficacy of a selegiline transdermal system (STS) in the treatment of patients with recurrent depressive episodes.

Methods: A secondary analysis was conducted using pooled data from two pivotal randomized, double-blind, placebo-controlled studies in adult outpatients with major depressive episodes. Analysis was restricted to those patients with a history of recurrent depression (n= 305; Nplacebo= 158; NSTS =147). Remission was defined as achieving a total score of ≤7 on the Hamilton Depression Inventory-17 (HAMD17) at the end of study assessments (week 6). Remission rates were calculated using last observation carried forward (LOCF). Differences in baseline characteristics across studies were tested using ANOVA and Chi-square tests. The Breslow-Day test was used to test homogeneity of odds ratios of remission across sites for each study as well as the odds ratio of remission across the studies. Odds ratios of remission were combined using the Mantel-Haenszel method. A logistic regression model was estimated for the treatment effect adjusting for study, age, gender and baseline HAMD17 total scores as a sensitivity analysis.

Results: Age, gender, and HAMD17 scores for patients with recurrent depression were not significantly different across the two trials. The Breslow-Day test did not reject the null hypothesis of homogeneity in odds ratio of remission across sites in each study or across the two studies, allowing for pooling of data. The combined odds ratio for STS vs. placebo for remission in the pooled data was 2.44 (95% Confidence Interval [CI] 1.25, 4.74). The logistic regression model also found an odds ratio of 2.44 (95% CI 1.25, 4.75) with no covariates being statistically significant.

Conclusions: Patients with recurrent depression treated with STS were more than twice as likely to achieve remission than placebo-treated patients. Availability of long-term treatment options for patients may improve the humanistic and economic burden associated with recurrent depression.

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Session II - 45

A Comparison of Tolerability Profiles of Patients with Major Depressive Disorder Receiving Selective Serotonin Reuptake Inhibitors (SSRI) in a Naturalistic Clinical-Care Setting

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Background: Most of the data regarding side effects of selective serotonin reuptake inhibitors (SSRIs) are derived from short term research trials with protocol-driven entry criteria. The objective of this study is to compare the tolerability of monotherapy with SSRIs in patients with a major depressive disorder (MDD) in a real-world clinical setting.

Methods: Data were captured by the Clinical Research Information System (CRIS) from 1999 through 2004 at the Duke University Medical Center. CRIS is an Electronic Psychiatric Medical Record Repository tool used for all clinical and research activities. The study cohort included 2292 with MDD who received SSRI monotherapy and attended at least two visits. Tolerability measures included physicians' assessments of side effects and the duration of treatment and compared across sertraline (n=719), citalopram (n=431), escitalopram (n=298), fluoxetine (n=499), and paroxetine (n=345) groups.

Results: Medications were generally well tolerated. The highest rates for any side effects were for citalopram (27%), followed by paroxetine (23%), escitalopram (19%), fluoxetine (19%), and sertraline (15%) (chi-square =23.07, $p<.001$; $p<.05$ for sertraline vs citalopram and sertraline vs paroxetine). Comparisons favored sertraline over citalopram for nausea, sedation, and sexual dysfunction (all p values <.05) and sertraline over paroxetine for sexual dysfunction ($p<.05$). There were no significant differences across the SSRIs for other side effects. Sertraline and fluoxetine had a significantly longer duration of treatment compared to escitalopram (hazards ratio = 1.24, chi-square =5.58, $p<.02$). The mean doses (mg/day) were: sertraline=118, citalopram=36, escitalopram=17, fluoxetine=41, and paroxetine=34.

Conclusions: SSRIs were generally well tolerated in a major depressed cohort in a clinical setting. However, compared to sertraline, citalopram patients appear to experience higher rate of side effects (in particular, nausea, sedation, and sexual dysfunction), and paroxetine patients experience more sexual dysfunction.

Session II - 46

A Pilot Test of an Adolescent Version of the Quick Inventory of Depressive Symptomatology Using Voice Recognition Technology

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Background: The assessment of adolescent depression relies on dated and time-intensive instruments that assess constructs not among the DSM-IV criteria for a major depressive episode. Current adolescent depression assessments also primarily use paper-and-pencil formats, when adolescents may be more comfortable with technology-based assessments. In adults, an Interactive Voice Response (IVR) version of the Quick Inventory of Depressive Symptomatology (QIDS IVR) has shown to be reliable, valid, unifactorial, and sensitive to change. An adolescent version of the QIDS was created by simplifying the language, leveling response burdens to discourage patterned responding, and including an irritability item to reflect DSM-IV criteria for pediatric depression. This assessment, the QIDS-A IVR, also used speaker-independent voice recognition technology.

Methods: The current study included 17 adolescents ranging from 12 to 16 years and 65% females. In addition to the QIDS-A IVR, clinician-rated and self-report versions of the QIDS (QIDS-C and QIDS-SR) and the Children's Depression Rating Scale-Revised (CDRS-R) were administered during a single office visit. The speech-enabled QIDS-A IVR permitted spoken responses, such as "yes," "no," and whole numbers. If the system did not recognize a response, the adolescent was asked to say the word again. If the system still did not recognize the response, the adolescent was instructed to input the response using the keypad on the telephone.

Results: Cronbach's alpha of the QIDS-A IVR in this study was .91. The QIDS-A IVR correlated significantly with the QIDS-C (r= .96), the QIDS-SR (r= .81), and the CDRS-R (r= .84). On average, the QIDS-A IVR required adolescents 6.25 minutes to complete (SD= 57 seconds). The voice recognition technology correctly identified the adolescents' spoken words in 93% of the 272 spoken responses. Of the remaining unrecognized responses, 2% were for yes responses, 4% for no responses, and 1% for whole number responses. One adolescent was asked to use the keypad for one question requiring a response of a whole number, but subsequently finished the assessment using speech input. The system was able to recognize a response from all adolescents on all items.

Conclusions: This study supports the feasibility of the QIDS-A IVR as a novel, reliable, and valid measure of adolescent depression severity. Adolescents navigated the assessment easily and quickly. The QIDS-A IVR may provide clinicians and researchers with a sound, technology-based method of assessing adolescent depression.

Session II - 47

Effects of Sertraline on Suicidal Thinking and Behavior in Late-Life Depression

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Background: The possible emergence of suicidal thinking or behavior during antidepressant treatment in children and adolescents has recently received considerable attention. Yet completed suicide remains more common in the elderly than in younger patients. In this report, we examine changes in suicidal thinking and behaviors in the largest placebo-controlled study of an antidepressant in late-life depression.

Methods: This is a secondary analysis of an 8-week, placebo-controlled, double-blind study of sertraline in patients 60 years of age and older with DSM IV major depression and a Hamilton Depression Rating (HAMD) score > 17. Details of the study have been previously published. Briefly, patients were randomized to 8 weeks of sertraline 50-100 mg/day or placebo. Outcome was assessed with the 17-item HAMD. Patients with marked suicide risk were excluded. All serious adverse events and adverse events (AEs) leading to discontinuation were reviewed to determine an association with suicidal ideation (SI) or behavior. Item 3 on the HAMD (suicidal thinking and behavior) was assessed in all subjects who received at least one dose of medication and had one post-treatment assessment.

Results: A total of 752 patients entered the study and 747 received at least one dose of medication. The mean age of the sample was 69.8 years (range 59-97) and 56% were female. As previously reported, significantly higher response rates were observed for sertraline than placebo. There were no completed suicides or suicide attempts during the trial. Only one serious adverse event during the trial (hospitalization) was associated with an increase in SI. No other AEs resulting in discontinuation were associated with SI. Ratings of SI on HAMD item 3 progressively declined during the trial. At endpoint, ratings on item 3 were lower in the sertraline group than in the placebo group, but did not reach statistical significance, (Wald chi-square, $p=0.059$, adjusted OR = 0.727; using ordinal logistic regression). In 252 patients with a HAMD item 3 score=0 at baseline, the percentage of patients who reported SI (item 3) at 2 weeks did not differ in the two groups.

Conclusions: There were no completed suicides or suicide attempts during the trial. Mean suicidal thinking ratings progressively declined in both groups. Emergence of new SI was similar in the sertraline and placebo groups.

Session II - 48

Impact of Residual Symptoms on the Risk of Recurrence During Maintenance Treatment of Late-Life Depression

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Objective: To assess the impact of overall burden of residual symptoms and of specific symptom clusters (core mood symptoms, sleep disturbance, and anxiety symptoms) on the risk of recurrence during maintenance treatment of late-life depression.

Methods: We analyzed data from a randomized clinical trial of maintenance treatment in patients with unipolar depression aged >69, 116 of whom remitted and remained stable during open pharmacotherapy and interpersonal psychotherapy (IPT) and were randomized to clinical management/pharmacotherapy; clinical management/placebo; monthly maintenance IPT/pharmacotherapy; or monthly maintenance IPT/placebo. We used Hamilton Depression Rating Scale (HAM-D) symptom clusters to measure residual core mood symptoms (depressed mood, guilt, suicidality, energy/interests), sleep disturbance (early, middle, late insomnia), and anxiety (agitation, psychic and somatic anxiety, hypochondriasis). Sleep quality was also assessed with the Pittsburgh Sleep Quality Index (PSQI). HAM-D score of >14 and meeting DSM-IV criteria for a major depressive episode defined recurrence. We used univariate Cox proportional hazards regression models controlling for antidepressant medication versus placebo to identify predictors of recurrence. We further employed a multiple Cox regression model controlling for other identified predictors of recurrence.

Results: In univariate models, total burden of residual symptoms anxiety (HAM-D) as well as sleep disturbance (PSQI but not HAM-D) predicted recurrence. HAM-D residual anxiety and PSQI residual sleep disturbance remained significant co-variates in a multiple Cox regression model, controlling for assignment to paroxetine or placebo.

Conclusions: In patients with late-life depression, who have remitted with pharmacotherapy and psychotherapy, residual anxiety and residual sleep disturbance predict recurrence of depression.

Session II - 49

Measures of Depression Severity and Treatment Response in Speech Obtained Using Interactive Voice Response (IVR) Technology

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Background: Current depression assessment methods rely on subjective judgments of symptom severity and/or change provided by a clinician or patient self-report. Subtle changes in eye movements and speech characteristics have been suggested as potential biomarkers of central nervous system disorders, possibly providing physiologically based indicators of disease severity. Previous research has found that the speech of depressed patients, obtained during clinical interviews, shows measures of motor timing (speaking rate and pause time) and frequency modulation (pitch variability) that are correlated with depression severity. Such speech measures can be obtained over the telephone using interactive voice response (IVR) technology.

Methods: Thirty-five physician-referred subjects (20 women, 15 men; Mean = 41.8 years) beginning treatment for depression were recruited into a six-week observational study. Subjects were assessed weekly via IVR (HAMD and QIDS) and biweekly by an expert clinician (HAMD). Standardized speech tasks were administered weekly via IVR. Vocal acoustic measures were extracted from the recorded speech samples. The internal consistency and convergent validity of the speech measures obtained were analyzed and compared with the conventional clinical measures of depression severity.

Results: The IVR and clinician HAMDs correlated .90, and correlated with the IVR QIDS .84 and .82, respectively. Depression severity declined over the six-week study period; 41% of the subjects responded to treatment (Week 6 HAMD ≤ 50% baseline). Total speech recording lengths, cumulative pause time, pause variability, and measures of speaking rate were marginally reliable (Cronbach's alphas .57 to .71) and correlated significantly with depression severity measures in expected directions (less depressed subjects spoke more quickly with less pausing, p-values < .01). Patients who responded to treatment had significantly greater pitch variability about the fundamental voice frequency, paused less while speaking, and spoke faster than they had at baseline (p-values < .05). Patients who did not respond to treatment did not show similar baseline to end-point changes in vocal acoustic measures. Telephone standardization for obtaining voice data was identified as a critical methodological factor influencing data quality.

Conclusions: This study extends previous research with a larger sample and assesses change associated with treatment. The feasibility of computer-automated telephone data collection to obtain reliable and valid voice acoustic measures of depression severity and treatment response is established. Analysis of speech acoustic properties provides a natural intersection in applied research for relating objective, physical manifestations of performance to subjective clinical observations of clinical status.

Session II - 50

Prevention of Depression Recurrence by Escitalopram Is Not Attributable to Potential Drug Discontinuation Effects

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Background: Escitalopram is efficacious and well-tolerated in the prevention of depression recurrence. However, when utilizing a randomized withdrawal design it is challenging to differentiate between depression recurrence and potential discontinuation symptoms in placebo-treated patients. The present analyses test whether potential discontinuation effects confounded the findings of an escitalopram depression recurrence trial.

Methods: A total of 234 patients with recurrent major depression (at least two previous episodes; baseline MADRS score $\geq$ 22) responding (MADRS score $\leq$ 12) to treatment in a lead-in trial received 16 weeks of flexible-dose, open-label escitalopram (10-20 mg/day) treatment. A total of a 164 (70%) patients completed the open-label phase and 139 (85%) patients maintaining response criteria were randomized to 52 weeks of fixed-dose, double-blind treatment with escitalopram (10-20 mg/day; N=73) or placebo (N=66). The primary efficacy parameter was time to depression recurrence, defined as a MADRS score $\geq$ 22 or insufficient therapeutic response.

Results: The primary analysis demonstrated a clear beneficial effect in patients who received maintenance treatment with escitalopram compared with patients switched to placebo treatment (Hazard Ratio [HR]=0.26, 95% CI: 0.13 to 0.52, P<0.001). Cumulative recurrence rates were lower for escitalopram-treated patients compared with patients receiving placebo (27% versus 65%, respectively). The incidence of treatment-emergent adverse events (TEAEs) during the first 14 days of double-blind treatment was 40.9% in placebo-treated patients and 20.5% in the escitalopram treatment group. In the subsequent 14-day period, the incidence of TEAEs was comparable between the placebo and escitalopram groups (42.2% and 37.0%, respectively), suggesting that discontinuation symptoms were largely diminished by this time. The beneficial effect of escitalopram maintenance treatment was still evident even after censoring of all patients with depression recurrence within 14 days of the start of double-blind treatment (HR=0.29, 95% CI: 0.14 to 0.59, P <0.001). Likewise, the primary result remained statistically significant when patients with any drug withdrawal-related TEAE during the first 14 days of double-blind treatment were removed from the analysis (HR=0.26, 95% CI: 0.12 to 0.54, P =0.0004).

Conclusions: Escitalopram was highly effective in prevention of depression recurrence in this study. The prophylactic effects of escitalopram observed cannot be attributed to any potential discontinuation symptoms in patients in the placebo group.

Session II - 51

Pharmacogenomics from the Atypical Depression Study Participants' Perspective

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Background: In November 2003 the FDA issued, for comment purposes only, "Guidance for Industry—Pharmacogenomic Data Submissions: Draft Guidance." FDA Commissioner McClellan stated, "Pharmacogenomics holds great promise to shed scientific light on the often risky and costly process of drug development, and to provide greater confidence about the risks and benefits of drugs in specific populations." Are the depressed clinical study patients who are refusing to provide their DNA possibly more representative of the depressed population at large? Moreover, if pharmacogenomics is to ultimately fulfill its promise in a conventional clinical environment, what can we learn from depressed study patients who say "no" to anonymous genotyping in a research environment?

Methods: We identified 16 depression studies which included genotyping, involving 304 randomized patients. While 95% of those patients [n=289] voluntarily agreed to genotyping, 15 patients refused. We conducted semi-structured interviews with patients who refused to volunteer for the pharmacogenomic research. Consistent with the exploratory nature of this research, our IRB-approved survey instrument consisted of both forced-choice (yes-no) and open-ended questions.

Results: The results of our research indicated that 100% of the patients refusing to provide a DNA sample reported (having had) no concerns or problems with the applicable informed consent forms; similarly, none of the patients reported refusing because of moral or religious beliefs. 80% of the patients reported having never heard about pharmacogenomics prior to reading the study-related consent form(s); nonetheless, 100% of the patients reported that, in their opinion, pharmacogenomics has more positive than negative potential for the future of medical care. 20% of the patients reported concerns about potential discrimination from an insurance company and 20% reported concerns about the lack of results (ever) being made available to them as a problem. 40% of the patients also reported that the results of genetic testing could potentially lead to some form of discrimination, and 60% of the patients reported that confidentiality was a concern.

Conclusions: While clinical study participants are considered to be more (medically) enlightened and professionally trusting than the average individual, we believe that the insights garnered from this pilot study are relevant to the population at large. Substantive recommendations for future researchers and clinicians, based on the narrative responses received from this pilot study sample, will also be presented.

Session II - 52

Impact of Low vs. High Dose Olanzapine or Risperidone on Outcome and Side Effects in Non-Psychotic Treatment-Resistant Depression

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Background: There are few head-to-head comparisons of the efficacy and tolerability of atypical antipsychotics as adjunct treatments in treatment-resistant depression (TRD)

Methods: In this randomized, double-blind, flexible-dose study, patients with non-psychotic, unipolar major depression who had failed an adequate trial of an SSRI or venlafaxine received either add-on olanzapine (2.5-15 mg) or risperidone (0.5-3 mg) while antidepressant doses remained unchanged. Patients were assessed weekly for improvement using the Hamilton Rating Scale for Depression (HRSD) and for side-effects over 6 weeks.

Results: Forty-three patients (OLZ n=22, RISP n=21) were included in analyses. Groups were subdivided into low dose (RISP-LO 0.5-1 mg n= 10, OLZ-LO 2.5-5 mg n=9) and high dose (RISP-HI 2-3 mg n=11, OLZ-HI 10-15 mg, n=13) categories. In terms of response as measured by 40% reduction in HSRD score after 6 weeks, both low dose groups did better than the high dose groups, but there was no significant difference found between drugs (OLZ=RISP). In the analysis, the median number of side-effects was 3. A comparison of the low dose groups to high dose groups did not show a significant difference in side-effect burden (p=0.390), but a comparison of the drugs showed that patients on olanzapine had significantly more side-effects (p=0.046). Analyses of patients with EPS-like side-effects found no significant difference between drugs (p=0.578) or in drug by dose interaction, although there was a trend for more EPS in the RISP-LO group (p=0.063). Analysis of weight gain over the 6 weeks showed a significant main effect of time (p<0.01) and a significant time by drug interaction where patients on olanzapine gained more weight (p<0.01), although there was no significant difference found in a time by dose-category interaction (p=0.504).

Conclusions: The findings suggest olanzapine or risperidone have similar efficacy when used as adjunctive medication in TRD. There may be some differences in adverse event profile, but these do not appear to be significantly influenced by dose.

Session II - 53

Genetic Polymorphisms in the Treatment of Depression: Speculations from an Augmentation Study Using Atomoxetine

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Objective: Despite adequate trials of pharmacological treatment using selective serotonergic reuptake inhibitors, a significant subset of patients with depression fail to fully respond and remain impaired in their mood and functioning. Previous studies have suggested that treatment resistance in depression may be related to polymorphisms (s/s allele) in the promoter region of the serotonin transporter gene (5HTTPR) or to dysregulation of multiple neurotransmitter systems, particularly norepinephrine. The present study examined the role of 5HTTPR genotype in a study of open-label sertraline treatment followed by augmentation with either atomoxetine (ATX) a selective norepinephrine reuptake inhibitor, or placebo in a double-blind, randomized design.

Methods: The key inclusion criteria were age 18 years or older, current diagnosis of major depression, at least one prior depressive episode in the previous 3 years, and baseline symptom severity rating ≥18 on the Hamilton Depression Rating Scale. There were 275 patients who received sertraline (SER, 100-200 mg/day) for 8 weeks. After this period, patients who remained symptomatic (total score >4 or >1 on any individual item of the Maier-Philipp core mood severity subscale of HAMD-17) were randomly assigned to augment their sertraline with either atomoxetine (40-120 mg/day) or placebo (PBO) for an additional 8 weeks.

Results: Of 276 patients starting the study, 146 patients remained symptomatic after 8 weeks of SER treatment (final dose, mean±SD: 161.1±43.4 mg/day). These poor treatment responders continued with SER and were randomly assigned to ATX or placebo. At study endpoint, treatment groups did not differ in mean changes on any measure of symptom severity or remission rates (SER/ATX: 29/72 [40.3%]; SER/PBO: 28/74 [37.8%], P=.87). 5HTTPR genotype was available from 261 patients, with 82 having the l/l or l/xl genotype; 120 having the l/s or xl/s genotype; and 51 having the s/s genotype. Genotype did not predict response to sertraline monotherapy or discontinuation rates. Following randomization, atomoxetine was associated with significantly more remissions compared with placebo for the s/s genotype (SER/ATX 9/11 [81.8%] vs. SER/PBO 5/14, [35.7%], P=.042). No treatment effects were observed in patients with other genotypes.

Conclusions: In patients with depression who either were poor-or nonresponders to sertraline treatment, the addition of atomoxetine did not improve significantly the response to treatment. Given the small sample of patients with the s/s allele, the observed relationship between genotype and the augmentation response must be considered speculative, but does merit further examination in additional studies.

Session II - 54

Pooled Analysis of Remission Rates Following Monotherapy with Bupropion or a Selective Serotonin Reuptake Inhibitor: Impact of Additional Data

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Background: Remission is widely believed to be the best criterion by which to compare the efficacy of antidepressants. A previous meta-analysis demonstrated that bupropion has remission rates comparable to selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder (MDD). We hypothesized that this finding would not be changed by including new additional data sets.

Objective: We now report a further meta-analysis of remission rates during treatment with bupropion or an SSRI, including data from two recently completed studies comparing bupropion and the SSRI escitalopram.

Methods: Data were pooled from nine randomized, double-blind, acute-phase studies of MDD. Patients received bupropion XL 300-450mg/day (n=276), bupropion SR 100-400mg/day (n=688), bupropion IR 225-450mg/day (n=60), escitalopram 10-20mg/day (n=281), fluoxetine 20-60mg/day (n=348), sertraline 50-200mg/day (n=358), paroxetine 10-40mg/day (n=52), or placebo (n=797). Remission rates (17-item Hamilton Rating Scale for Depression score =7) were calculated at week 8 or endpoint using pooled data from all nine studies and separately for the six studies that included a placebo control.

Results: Remission rates for the analysis of all studies were 46% for bupropion, 46.8% for SSRIs, and 35.5% for placebo (statistical equivalence within 5%). Remission rates for both active treatments were superior to placebo ($p<0.001$). For the subset of studies that included a placebo control, remission rates were 44% for bupropion, 45% for SSRIs, and 36% for placebo ($p<0.001$ bupropion and SSRIs v. placebo). The five active treatments were well tolerated and showed similar overall frequencies of adverse events. However, the SSRIs, including escitalopram, were associated with a greater incidence of orgasm dysfunction, sexual arousal disorder, and sexual desire disorder compared to bupropion and placebo.

Conclusions: Bupropion monotherapy produced similar remission rates as the SSRIs. All medications were well-tolerated; however, SSRI therapy resulted in higher rates of sexual dysfunction compared to bupropion and placebo.

Session II - 55

Magnetic Seizure Therapy: Clinical Efficacy and Safety of a Novel Neurostimulation Treatment

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Background: The primary aim of this study was to evaluate the safety and efficacy of magnetic seizure therapy (MST), a novel form of neurostimulation treatment, in treating patients with major depressive disorder (MDD).

Methods: Twenty patients meeting DSM-IV criteria for major depressive disorder received acute course MST in this two-center trial of efficacy and safety of MST in treating major depressive disorder. These patients had an average age of 46.7 ± 9.9 years; 40% were female, and 15% were diagnosed with psychosis. $HRSD_{24}$ and the $IDS\text{-}SR_{30}$ measurements were obtained at baseline and endpoints for all participants. Global improvement was measured by the CGI. Treatment side effects were measured after each treatment by the Columbia ECT Subjective Side Effects Questionnaire. All patients received comprehensive neuropsychological evaluation before, during, and after MST, which were z-transformed relative to the distribution of baseline scores. Frequency and descriptive analyses were computed for categorical variables. For within group comparisons of continuous variables, paired, pooled t-tests were conducted.

Results: After 9.0 ± 2.8 MST treatments, a significant decrease in depression severity and marked improvement in clinical symptoms was evidenced by a mean change in $HRSD_{24}$ from baseline to end of $46.7 \pm 28.0\%$. Response and remission rates were 60% and 35%, respectively ($> 60\%$ reduction from baseline $HRSD_{24}$ score and final $HRSD_{24}$ < 10). 45% of patients showed sustained benefit 2-weeks post end treatment. Patients were found to have low global cognitive impairment, retrograde amnesia, and high recovery of orientation post MST, with minimal physical side effects.

Conclusions: This study showed that MST is a safe and efficacious form of neurostimulation treatment. MST showed clinically meaningful antidepressant effects in patients with unipolar MDD, while producing a benign cognitive side-effect profile. Further research is needed to refine and optimize MST as an antidepressant treatment modality.

Session II - 56

Validation of the GRID-Hamilton Depression (GRID-HAMD) Rating Scale

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Background: The GRID–Hamilton Depression Rating Scale (GRID-HAMD) is a standardized scoring system that operationalizes intensity and frequency of depressive symptoms, allowing these dimensions to be rated simultaneously to arrive at a HAMD severity score. The scale has been tested for usability and reliability. This study examined the validity of the GRID-HAMD by comparing total and item scores of the GRID-HAMD to the Structured Interview Guide for the HAMD (SIGH-D). Inter-rater reliability of the GRID-HAMD, SIGH-D, and the Guy version of the HAMD were compared.

Methods: A total of 150 outpatients (from 10 U.S. research sites) diagnosed with a DSM-IV-defined depressive disorder participated in this study. Subjects were each administered a version of the HAMD twice, by two independent interviewers, on the same day. Raters were blind to each others' scores. Subjects were randomly allocated to one of 4 arms: GRID vs. SIGH-D (n=60), GRID vs. GRID (n=30), SIGH-D vs. SIGH-D (n=30), and GUY HAMD vs. GUY HAMD (n=30). Raters (N=29) had an average of 20 years' clinical experience and 13 years' experience administering the HAMD.

Results: The intraclass correlation (ICC) for subjects receiving two GRID-HAMDs was .9354 (95% CI .8714, .9682), p < .0001. The ICC for subjects receiving two SIGH-Ds was .9504 (95% CI .8981, .9763), p < .0001, and for subjects receiving two GUY HAMDs .7783 (95% CI .5740, .8920), p < .0001. The ICC using the GRID-HAMD was significantly greater than the ICC using the GUY HAMD (z=3.4461, p = .0006). Similarly, the ICC with the SIGH-D was significantly greater than the ICC with the GUY HAMD (z=4.0889, p=.0004). The ICCs for the GRID-HAMD and SIGH-D were not significantly different (z=0.7254, p=.46818). The ICC between the GRID and SIGH-D was .8169 (95% CI .7119, .8862), p < .0001; mean score difference between the GRID-HAMD and SIGH-D in subjects who received both interviews was not significant (mean difference = 0.20 points, t(59)= 0.397, p=.693).

Conclusions: The GRID-HAMD and the SIGH-D, which are semi-structured interviews, demonstrated excellent IRR compared to the unstructured Guy version, which was significantly lower than either scale. The GRID-HAMD is as reliable as the current HAMD "gold standard" (SIGH-D) and has several advantages: a standardized scoring system and conventions and interview guide integrated within the instrument. These features may provide specific benefits for typical raters who have less clinical and assessment experience than the highly experienced raters in this study.

Session II - 57

Two-Year Maintenance Treatment Study to Assess Recurrence Prevention with Venlafaxine XR in Patients with Recurrent Unipolar Major Depression

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Background: Second-year results from a 2-year maintenance phase of a long-term study to evaluate efficacy and safety of venlafaxine extended release (XR) in preventing recurrence of depression.

Methods: Outpatients with recurrent unipolar depression (N=1096) were randomly assigned in a 3:1 ratio to 10-week treatment with venlafaxine XR (75-300 mg/day) or fluoxetine (20-60 mg/day). Responders (HAM-D$_{17}$ total score ≤12 and ≥50% decrease from baseline) entered a 6-month, double-blind, continuation phase on the same medication. Continuation phase responders enrolled into the maintenance treatment consisting of two consecutive 12-month phases. At the start of each maintenance phase, venlafaxine XR responders were randomly assigned to receive double-blind treatment with venlafaxine XR or placebo, and fluoxetine responders were continued for each period. We report results from the second 12-month maintenance phase, which compared the time to recurrence of depression with venlafaxine XR versus placebo as the primary efficacy measure. The primary definition of recurrence was a HAM-D$_{17}$ total score >12 and <50% reduction from baseline (acute phase) HAM-D$_{17}$ at two consecutive visits or at the last valid visit prior to discontinuation.

Results: The cumulative probabilities of recurrence through 12 months in the venlafaxine XR (n=43) and placebo (n=40) patients who had been responders to venlafaxine XR during the maintenance phase were 8.0% (95% CI: 0.0, 16.8) and 44.8% (95% CI: 27.6, 62.0), respectively (P<0.001, log rank test). Overall discontinuation rates were 28% and 63% in the venlafaxine XR and placebo groups, respectively. Adverse events were the primary reason for discontinuation for one patient (2%) in the venlafaxine XR group and four (10%) in the placebo group.

Conclusions: An additional 12 months of maintenance therapy with venlafaxine XR was effective in preventing recurrence of depression in patients who had been responders to venlafaxine XR after acute (10 weeks), continuation (6 months), and the initial maintenance (12 months) therapy.

Session II - 58

Bupropion XL's Steady-State Pharmacokinetics in Children

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Background: A newer extended-release (XL) form of the antidepressant (BUP) bupropion is reported to allow once-daily dosing in adults, but its pharmacokinetics have not been well-studied in children.

Methods: Eligible subjects were physically healthy psychiatric outpatients ranging from 7-17 years old, weighing >30 kg, and prescribed bupropion XL monotherapy at doses of 150 mg or 300 mg/d for >13 days. Subjects were hospitalized for 24 hours at the General Clinical Research Center at Children's Hospital of Pittsburgh and had serial blood draws every 1.5 to 3 hours from an IV port. Concentration versus time data were fitted for each subject's plasma levels, using descriptive, model-independent analysis for the parent-compound bupropion, and a two-exponential, one-compartment model for three active metabolites: hydroxybupropion (HB), threohydrobupropion (TB), and erythrohydrobupropion (EB).

Results: The final sample consisted of six boys and four girls, ages 11-16 years old. Two subjects were black and eight others white. The sample's mean weight was 70.5 + 15.8 kg. The median duration on studied doses of bupropion was 21 days. Five were studied on 150 mg/d and another five on 300 mg/d doses. The mean half-life of BUP was 16.4 + 6.7 hrs. The mean Tmax of BUP was 4.8 hours. All concentration parameters, including areas under the curves to 24 hours (AUC) and maximum concentrations (Cmax), were approximately doubled in subjects taking doses of 300 mg/d compared to 150 mg/d. AUC ratios of metabolites to BUP were: HB:BUP = 16, TB:BUP = 5, and EB:BUP = 1. Relative to our previous sample of 19 youths taking bupropion SR, mean Cmaxs in the current sample (adjusted to doses of 150 mg/d) were 15% lower for HB and 42%, 43%, and 45% lower for BUP, TB, and EB, respectively, with differences other than for HB reaching significance (p<.05).

Conclusions: Results are consistent with previous reports of bupropion having linear pharmacokinetics. BUP's mean half-life was approximately 20% shorter than that reported for adults in the product label. Relative to a previous study of bupropion SR in youth, the Tmax of BUP was 1.5 hours longer. The lower Cmaxs of BUP and metabolites may improve this medication's tolerability. Our findings suggest that a once-daily dosing schedule is appropriate in youths prescribed bupropion XL and that active metabolites such as HB may be particularly important given their higher and more sustained levels than the parent compound.

Session II - 59

Paroxetine CR in Late-Life Depression: The Role of Self-Report Scales

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Background: Self-report scales are frequently used to augment clinician-rated scales in assessing antidepressant efficacy. These scales may confirm treatment results and provide additional insights into drug response from the patient's perspective.

Methods: This was a double-blind, placebo-controlled trial evaluating fixed low doses of paroxetine CR in depressed outpatients > 60 years old. A one-week placebo run-in preceded randomization to placebo, paroxetine CR 12.5mg, or 25mg daily for 10 weeks.

Eligibility included a diagnosis of major depression and a baseline Hamilton Depression Rating (HAM-D) > 18. Patients with other axis I disorders, or those requiring other psychotropics, were ineligible. The primary efficacy variable was change from baseline in the HAM-D. Self-report secondary measures were: the Geriatric Depression Scale (GDS-15), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Q-LES-Q "Overall Life Satisfaction;" and assessments of overall pain, headache, "Arms, Hands, Legs and Feet (AHLF)", and pain "Interference with Activities of Daily Living (ADL)," Adverse experiences (AEs) and AE withdrawals comprised the safety assessments.

Results: The intention-to-treat (ITT) population included 515 patients who were predominantly Caucasian (82%) and female (61%) with a mean age of 67. The HAM-D endpoint LOCF analysis showed mean changes of -12.1 for 25mg, -10.7 for 12.5mg and –8.9 for placebo. The drug/placebo differences were statistically significant for both active treatments (25mg: $p<0.001$, 95% C.I. = [-4.8, -1.7]; 12.5mg: $p=0.029$, 95% C.I. = [-3.4, -0.2]). The week 10 GDS analysis also showed statistical significance for active treatments versus placebo (25mg: $p=0.002$; 12.5mg: $p=0.016$). The total Q-LES-Q showed statistical significance for paroxetine CR, as did the Q-LESQ "Overall Life Satisfaction" item. Overall pain, headache, and back pain were not statistically significant for active drug, although paroxetine CR 25mg was statistically significant in pain ratings for AHLF and ADL interference. Common AEs (> 5% and twice the placebo rate) for active treatments were somnolence, influenza and nasopharyngitis. AE withdrawals were low for all treatments (paroxetine CR 12.5mg=6%; paroxetine CR 25mg=8%; placebo=7%).

Conclusions: The self-report GDS supports clinical efficacy of paroxetine CR 12.5mg and 25mg daily doses as determined by the clinician-rated primary efficacy variable. Self-report quality-of-life and pain measures may elucidate this effect from a patient perspective.

Session II - 60

The Impact of Study Design on the Results of Continuation Studies of Antidepressant Medication

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Abstract: The return of symptoms of depression after a period of improvement lasting for a short time (less than six months) is referred to as a relapse. Many placebo-controlled studies have established that antidepressants are effective in preventing relapse. Continuation studies of antidepressants have used two designs. In most studies, all patients are initially treated with active medication, and then treatment responders are randomized to continue with the active medication or switch to placebo in a double-blind manner. Alternatively, some studies begin as a double-blind, placebo-controlled acute study, and responders to active treatment and placebo are continued on the treatment to which they responded. The goal of this presentation is to examine the impact of study design on the results of continuation studies.

We identified six continuation studies of antidepressants that began as placebo-controlled efficacy studies and continued the treatment responders on the medication to which they responded. Summing across studies, the relapse rate on placebo was 25.3%, more than three times higher than the relapse rate on active medication (7.8%). In contrast, the relapse rates were two times higher in studies beginning with an open-label trial followed by a double-blind continuation on active medication or switch to placebo. These findings suggest that the design of continuation studies impacts on the absolute rate of relapse. As will be discussed, this has implications for estimates of how much tachyphylaxis rates should be attributed to the loss of a true drug effect and how much might be represented by the re-emergence of symptoms in patients who were presumptive placebo responders.

Session II - 61

Change in Frontal EEG During First Week of SSRI Treatment Predicts Clinical Response in Major Depressive Disorder

Dan V. Iosifescu, M.D., M.Sc. [1], Scott D. Greenwald, Ph.D. [2], Charles P. Smith, B.S. [2], Philip H. Devlin, M.S. [2], Jonathan E. Alpert, M.D. [1], Maurizio Fava, M.D. [1]

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Background: Previously we reported interim results of a study suggesting that frontal EEG activity predicts antidepressant treatment response in subjects with major depressive disorder (MDD).[1] This report summarizes results from the completed trial.

Methods: Subjects meeting DSM-IV criteria for MDD entered an 8-week prospective treatment with open-label, flexible dose SSRIs. At each study visit (baseline, week 1, 4, and 8) we assessed MDD severity with the 17-item Hamilton Depression Rating Scale (HAM-D-17) and we recorded serial, 4-channel EEGs (F7-Fpz, F8-Fpz, A1-Fpz, A2-Fpz). An EEG index (Bis-Dep (rev 0.2)) was developed to predict clinical response using EEGs recorded at baseline and week 1. Clinical response was defined as HAM-D-17 reduction during treatment > 50%.

Results: Seventy-one subjects completed 8 weeks of treatment, while 13 subjects completed 4 weeks, yielding 84 subjects for analysis using last observation carried forward (mean age 36.1 + 12.9; 46.4 % female). Forty-six subjects (55%) responded to treatment. The EEG index predicted response with 73% accuracy overall (n=84). As expected, response prediction was better in the 22 subjects who had no antidepressant dose change after week 1 compared to the 62 subjects who had dose changes after the EEG assessments used to make the prediction (i.e., 86% vs. 68%, p <0.05). There was no significant difference between completers (N=71) and non-completers (N=13) in response rate (55% vs. 54%), fraction that received dosage adjustments (85 % vs. 72%), or EEG prediction accuracy (70% vs. 77%) (p > 0.05).

Conclusions: This study suggests that automated analysis of frontal EEG may predict treatment efficacy after one week of antidepressant treatment. The EEG index predictive ability is increased in subjects with no antidepressant dose change after week 1. We hypothesize the predictive accuracy in subjects receiving dosage adjustments might be enhanced by re-assessing the EEG index one week after each dose change. We are testing this hypothesis currently in a prospective evaluation of this EEG index in a large, multi-center trial.

Reference:
[1] Iosifescu D, et al: Frontal EEG predicts at one week predicts clinical response to SSRIs in MDD. 2005 APA Annual Meeting (#870).

Session II - 62

Social Functioning in Body Dysmorphic Disorder: Assessment Considerations

Elizabeth R. Didie, Ph.D. [1], Christina Tortolani, M.A. [2], Mary M. Walters, Ed.M. [2], William Menard, B.A. [2], Katharine A. Phillips, M.D. [1]

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Background: Individuals with body dysmorphic disorder (BDD), regardless of treatment status, have markedly poor social functioning and quality of life. Previous reports, however, may underestimate the extent of this impairment. Scoring on certain functioning measures, such as the Social Adjustment Scale-Self Report (SAS-SR), potentially excludes more severely ill individuals from some scale domains, thereby possibly underestimating functional impairment. While the developers of the SAS-SR have identified this exclusion of severely ill persons from certain domains as a potential limitation of the scale, the magnitude of this effect is unknown. It is not known how the proportion of subjects excluded from these domains compares across disorders and the extent to which their exclusion reflects psychopathology.

Methods: To explore this issue, 73 individuals with BDD who reported having no primary relationship (and were therefore excluded from scoring on the SAS-SR Primary Relationship domain) were compared to 58 individuals with BDD who had a primary relationship and were included in scoring on a number of functioning and quality of life measures.

Results: Subjects without a primary relationship had significantly poorer scores on SAS-SR Overall Social Adjustment (the scale's total score) than those with a primary relationship. In addition, those without a primary relationship reported significantly worse functioning on the SAS-SR Social/Leisure and Family Unit subscales. The group without a primary relationship also had significantly poorer functioning on the LIFE Global Social Adjustment scale. There was a trend for subjects without a primary relationship to have lower GAF scores as well as poorer quality of life on the Q-LES-Q total score and the Q-LES-Q social subscale. In addition, subjects without a primary relationship had greater severity of BDD and depressive symptoms at a trend level.

Conclusions: These findings suggest that despite the many strengths of the SAS-SR, it has an underrecognized limitation, which is that it may exclude more seriously ill individuals from scoring in certain domains. Thus, previous reports of psychosocial functioning in BDD may underestimate patients' actual degree of functional impairment. This underestimation may also pertain to other domains of functioning, to other disorders, and to certain other functioning and quality-of-life measures. Because of the importance of psychosocial functioning and its assessment, these issues deserve further investigation across a variety of disorders and scales.

Session II - 63

Comparison of the Responsiveness and the Reliability of the 17-Item Hamilton Depression Scale and the Geriatric Depression Scale in Elderly Patients with Major Depressive Disorder

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Background: The clinician-rated 17-Item Hamilton Depression Scale ($HAMD_{17}$) and the patient-rated Geriatric Depression Scale (GDS) are both validated scales used in the assessment of major depressive disorder (MDD). However, there is little information regarding the comparison of the performance of these two scales in elderly depressed patients. Using data from a placebo-controlled, randomized, parallel study comparing the selective serotonin and norepinephrine reuptake inhibitor duloxetine with placebo, with regard to changes in cognitive functioning in depressed patients >65 years old during 8 weeks of acute treatment, we compared the responsiveness and reliability of the HAMD and the GDS.

Methods: Clinically significant improvement in MDD was defined as >2 point reduction from baseline in a patient's Clinical Global Impressions of Severity (CGI-S) score at endpoint. Clinically unchanged patients, those not demonstrating significant clinical improvement or worsening, were defined by a change from baseline to endpoint in CGI-S of no more than ± 1 point. Responsiveness was assessed via effect size (ES) and Guyatt's Responsiveness Statistic (GRS). The reliability of the two scales was assessed using the intraclass correlation coefficient (ICC).

Results: The mean baseline scores on the HAMD and GDS for all randomized patients were 18.9 and 17.7, respectively; they correspond to the 36.3 and 59.0 percentile of each scales' respective range. The mean CGI-S score was 4.1 at baseline. Of the 311 randomized patients, 303 (97.4%) completed at least one post baseline visit and 242 (77.8%) completed the acute treatment phase. The ES for clinically significant improvement was 1.57 for the HAMD vs. 1.12 for the GDS. The GRS was 2.13 for the HAMD vs. 1.53 for the GDS. The ICC between the screening and baseline scores for all patients was 0.653 for the HAMD vs. 0.911 for the GDS, and the ICC between baseline and endpoint in clinically unchanged patients was 0.766 for the HAMD vs. 0.931 for the GDS.

Conclusions: The $HAMD_{17}$ demonstrated better responsiveness than the GDS through evaluation of ES and GRS for clinically significant improvement, suggesting the $HAMD_{17}$ has a better ability to detect clinically relevant interventional effects. Conversely, the GDS demonstrated better reliability through higher ICCs between pretreatment assessments and within clinically unchanged patients during treatment, suggesting reduced within-patient variability compared with the $HAMD_{17}$. Although both scales have advantages in this population, the use of the more administratively burdensome, clinician-rated $HAMD_{17}$, when strictly implemented with techniques that minimize within-patient variability, may reduce trial time and cost by requiring smaller sample sizes.

Poster # II - 64 was not presented at the meeting.

Session II - 65

Optimization of Acute Electroconvulsive Therapy: Comparing Bilateral and Right Unilateral ECT Augmented with Antidepressants

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Background: Optimal administration of electroconvulsive therapy (ECT) in the treatment of major depressive disorder remains unclear. The primary aim of this study was to evaluate the antidepressant efficacy of augmenting ECT with pharmacotherapy.

Methods: Three hundred thirty-eight participants were randomized in this multicenter, parallel-group, double-masked trial evaluating the efficacy of right unilateral (RUL) and bilateral (BL) ECT augmented with nortriptyline (NT), venlafaxine (VEN), or placebo. Participants (age 49.3 ± 15.8, 64% female) were stratified by resistance to antidepressant pharmacotherapy and the presence or absence of psychosis. Depression severity was measured by the 24-item Hamilton Rating Scale for Depression ($HRSD_{24}$) and neurocognitive functioning was assessed pre and post ECT. Remission was defined as two consecutive $HRSD_{24}$ scores ≤ 10.

Results: No significant difference was found between remission rates of patients receiving high dose RUL ECT or low dose BL ECT. However, patients randomized to NT and VEN augmentation showed a 15% greater remission rate ($p < 0.05$) than those receiving placebo. ECT effected memory functioning with those randomized to BL ECT showing more deficits than RUL ECT ($p < 0.05$) regardless of antidepressant augmentation. Medication assignment effected attentional processes with those patients receiving NT showing improvement compared to VEN or placebo ($p < 0.05$) regardless of ECT.

Conclusions: This study demonstrated that ECT augmented with antidepressant pharmacotherapy alters the clinical efficacy and neurocognitive outcome. Both types of ECT provided equivalent remission rates; however, BL showed more negative impact on memory than did RUL.

Session II - 66

Characterization of the Placebo Response in the Hypericum Depression Trial Group's Study

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Objective: Natural antidepressants such as hypericum (St. John's Wort) have been suggested to exert their effect in part due to a strong placebo effect. The Hypericum Depression Trial Study Group (2002) recently investigated hypericum for treatment of depression. Among 340 subjects treated for 8 weeks with hypericum, sertraline, or placebo, there was no significant benefit of either drug over placebo. We sought to re-examine this database with a particular focus on the placebo arm (n=116) to further characterize placebo response in the context of alternative medicine trials.

Methods: Using a variety of statistical analyses, we examined the following hypothetical characteristics of the placebo arm: 1) Does most improvement in placebo recipients occur early in the course of treatment? 2) Does the presence of anxiety in depressed subjects dampen response to placebo? 3) Do somatic Hamilton-D Scale (HAM-D) symptoms respond to placebo at a lesser rate than psychological HAM-D symptoms?

Results: 1) Among placebo recipients (n=116), a mean HAM-D-17 score improvement of 21.3% occurred by the second week of treatment; 30.6% by week 4; and 51.8% by week 8. In this arm, 59% of the total mean improvement occurred by the first 4 weeks of treatment. Hypericum recipients (n=113) experienced 68% of total HAM-D-17 score improvement by week 4, and sertraline recipients (n=111) 66%. The differences between the three arms were not significant (p>0.05). 2) We found no significant difference in response rates among placebo recipients with anxious depression (n=13; 23% responders) compared to those without anxious depression (n=103; 48% responders) (Chi-squared =2.80, p=0.09). Similar results were obtained for sertraline and hypericum recipients (p>0.05). 3) We found significantly greater percent improvement in somatic symptoms (46.7%) than in psychological symptoms (40.2%) among placebo recipients (p<0.05) and hypericum recipients (44.3% vs 37.2%) (p<0.05). No significant difference in alleviation of psychological vs. somatic symptoms was observed in the sertraline arm (47.3% vs 46.4%; p>0.05).

Conclusions: Response patterns in placebo recipients were similar to those seen with hypericum and sertraline, suggesting that the major portion of improvement to antidepressants or placebo occurs within the first 4 weeks of treatment. The presence of anxiety did not significantly impact response to placebo or active drug in this sample, but somatic symptoms appeared to improve more significantly than psychological symptoms in placebo and hypericum recipients. Our results suggest that the impact of placebo response may be significant in the context of complementary and alternative medicine, and warrants further characterization.

Session II - 67

Treatment of Major Depressive Disorder with Desvenlafaxine Succinate

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Objective: This study evaluated the efficacy and safety of desvenlafaxine succinate (DVS) extended release in the short-term treatment of major depressive disorder (MDD).

Methods: Adult outpatients with DSM-IV MDD were randomly assigned to treatment with DVS 100 mg/day (n=114), 200 mg/day (n=116), or 400 mg/day (n=113), or placebo (n=118) for 8 weeks. The primary efficacy variable was the change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D_{17}) total score at the final on-therapy evaluation. The key secondary efficacy variable was the change from baseline in the Clinical Global Impression-Improvement (CGI-I) score. The visual analog scale (VAS-PI) overall score was used to evaluate pain improvement. Additional secondary variables included rates of response ($\geq$50% decrease from baseline HAM-D score) and remission (HAM-D_{17} $\leq$7). Adverse events, vital signs, and laboratory determinations were used to evaluate safety.

Results: At the final on-therapy evaluation, the reduction in HAM-D_{17} scores for the DVS 100 mg (-10.60) and 400 mg (-10.76) groups were significantly greater than for the placebo group (-7.65; P=0.0038 and P=0.0023, respectively); for the DVS 200 mg group, the reduction was -9.63 (P=0.0764). Results on the key secondary efficacy measure, CGI-I score, were significant for all groups. Response rates were significantly greater in the DVS 100 mg and 400 mg groups compared with placebo (P=0.017 and P=0.046, respectively). VAS-PI results were significant only for the 100 mg group versus placebo (P=0.002). The percentage of patients that discontinued due to adverse events was 13% for the DVS 100 mg group, 9% for the 200 mg group, 16% for the 400 mg group, and 3% for the placebo group. The most common treatment-emergent adverse event associated with DVS was nausea, and the overall tolerability profile was consistent with the SNRI class.

Conclusions: DVS is effective and generally well tolerated in the short-term treatment of MDD. These results are consistent with another recently completed randomized placebo-controlled study that demonstrated the efficacy of two fixed doses (200 mg and 400 mg) of DVS in treatment of MDD.

Session II - 68

Desvenlafaxine Succinate: Efficacy and Safety in the Short-Term Treatment of Major Depressive Disorder

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Objectives: Evaluate the antidepressant efficacy and safety of desvenlafaxine succinate (DVS) extended release in adults with major depressive disorder (MDD).

Methods: In a phase 3, multicenter, randomized, double-blind, parallel-group study, adult outpatients aged 18 to 75 with a primary diagnosis of MDD were assigned to treatment with fixed doses of DVS 200 mg or 400 mg daily, or placebo, for 8 weeks. The primary efficacy measure was change from baseline on the 17-item Hamilton Rating Scale for Depression (HAM-D$_{17}$); the key secondary efficacy measure was the Clinical Global Impression- Improvement (CGI-I) scale. Other secondary efficacy measures included response ($\geq$50% decrease from baseline HAM-D$_{17}$ score) and remission (HAM-D$_{17}$ $\leq$7), improvement on the visual analog scale-pain intensity (VAS-PI), and other symptomatic and functional outcomes. Safety was evaluated via assessment of adverse events (AEs), discontinuation due to AEs, physical examination, 12-lead electrocardiogram, vital signs, laboratory determinations, and the discontinuation-emergent signs and symptoms (DESS) checklist.

Results: A total of 375 subjects were randomly assigned to treatment; 373 were included in the safety analyses and 369 in the intent-to-treat efficacy analyses. At the final on-therapy evaluation, adjusted mean change from baseline in HAM-D$_{17}$ total score was greater for DVS 200 mg (-12.6, P=0.002) and DVS 400 mg (-12.1, P=0.008) than for placebo (-9.3). Mean CGI-I scores were lower for DVS 200 mg (2.2, P=0.004) and DVS 400 mg (2.3, P=0.028) than for placebo (2.7). Statistically significant differences versus placebo were observed with both doses on Montgomery-Asberg Depression Rating Scale and CGI-Severity scores, and HAM-D$_{17}$ response rates. DVS 200 mg was associated with significantly higher remission rates and greater improvement in VAS-PI overall score and some component scores compared with placebo. DVS 400 mg was associated with significantly greater improvement compared with placebo on some VAS-PI component scores. The most common adverse event associated with DVS treatment was nausea, and the overall profile was consistent with the SNRI class. Most AEs were mild or moderate in severity, and safety assessments revealed few clinically significant changes.

Conclusions: These data demonstrate the efficacy and safety of DVS 200 mg/day or 400 mg/day for the treatment of outpatients with MDD.

Session II - 69

A Bayesian Model to Analyze Patient Subsets with Non-Normal Distributions in Antidepressant Trials

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Background: Conventional methods to analyze treatment differences are based on an assumption of normality, which may be violated in clinical trials of special populations. Comparisons based on normality assumptions may not be appropriate and may result in inadequate power to detect treatment differences in the presence of outliers. Non-parametric methods using transformation of the raw data complicate data interpretation. An alternative approach using Bayesian methodology in the presence of outliers is described.

Methods: The adolescent (12 to 17 years) subset from two previously reported 8-week, randomized, double-blind, placebo-controlled trials in children and adolescents with major depressive disorder were retrospectively analyzed, to provide estimates of power for a subsequent planned trial. Study 1 compared citalopram 20-40mg/day (N=89) to placebo (N=85). Study 2 compared escitalopram 10-20mg/day (N=129) to placebo (N=132). In both studies, the Children's Depression Rating Scale-Revised (CDRS-R) was the primary efficacy outcome. Study 2 did not demonstrate efficacy of escitalopram. A post-hoc Bayesian model using the t-distribution with unknown degrees of freedom was used to assess the treatment effect.

Results: Analysis of the change in CDRS-R from Baseline to Week 8 for the adolescent subgroup using conventional meta-analytic methods yielded a least-square mean difference (LSMD, active treatment vs. placebo) of -4.6 (effect size=0.32, p=0.01). However, the distribution of the residuals was not normally distributed (Shapiro Wilks, p= 0.0027), violating assumptions of normality in standard methods of estimating treatment differences. Non-normality was also confirmed using the Bayesian method, yielding median estimates of the degrees of freedom of 12.09 in the escitalopram-treated group for Study 2. Using the post-hoc Bayesian model, the change in CDRS-R from Baseline to Week 8 in the active treatment group was statistically significantly different from placebo (LSMD = -5.1, effect size=0.35, p=0.007).

Conclusions: A Bayesian method generalizing the normal theory may provide an alternative approach to enhance the precision of estimated treatment effects and allow for the demonstration of a treatment effect in clinical trials with non-normal distribution outcomes.

Source of Funding: Forest Laboratories, Inc.

Session II - 70

Pharmacotherapy Effectiveness for Body Dysmorphic Disorder in a Prospective Observational Study: Preliminary Propensity-Adjusted Results

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Background: SRIs appear efficacious for body dysmorphic disorder (BDD), a severe and relatively common disorder. However, only two randomized controlled efficacy studies, no fixed-dose efficacy studies, and no prospective effectiveness studies have been conducted. Therefore, in this prospective observational study, we examined SRI effectiveness for a broadly inclusive sample of subjects largely treated in the community. In an observational study, treatment is not randomized, and, therefore, treatment effectiveness must account for the non-equivalent comparison groups to reduce the impact of selection bias.

Methods: One hundred eighty-five individuals with DSM-IV BDD participated in a prospective, observational, longitudinal study of BDD's course (mean follow-up duration=3.0 ± 0.9 years). Using the Longitudinal Interval Follow-up Evaluation (LIFE), weekly information was obtained on BDD symptoms, medications received, and doses. The analyses included 579 courses of treatment (including none). Improvement in BDD was defined as ≥ 1 point decrease in pre-post treatment ratings on the LIFE BDD-PSR, a reliable 7-point measure of BDD severity.

Results: The propensity for treatment intensity model (using mixed-effects ordinal logistic regression analyses) indicated that subjects who received more intensive SRI treatment (higher doses) tended to be male, older, have less severe symptoms, and have comorbid OCD. Treatment effectiveness analyses using mixed-effects logistic regression models were then conducted, separately for each propensity quartile; because there was no propensity-by-treatment interaction, these quartile-specific results were pooled. After controlling for propensity for treatment intensity, subjects who received lower SRI doses (<125 mg/day of sertraline, <20 mg/day of escitalopram, <40 mg/day of fluoxetine, paroxetine, or citalopram, and <150 mg/day of fluvoxamine or clomipramine) were significantly more likely to have improvement in BDD than those who received no SRI (odds ratio=1.49; 95% CI: 1.03-2.14; p=.034). Subjects who received higher SRI doses were not significantly more likely to improve than those who received lower SRI doses or no SRI.

Conclusions: Longitudinal propensity-adjusted analyses demonstrated that subjects who received a lower-dose SRI were more likely to report improvement in BDD symptom severity than untreated subjects over the course of treatment. These SRI doses are generally within the range often used for depression, but lower than often recommended for BDD. Longer follow-up and more courses of treatment will increase power and could improve the quality of prospectively observed variables included in the propensity model, which would further reduce selection bias. This will enable us to better examine whether higher SRI doses are more effective for BDD, as suggested by clinical experience and retrospective (lifetime) data from this sample.

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Pooled Analysis of Venlafaxine XR in the Short-Term Treatment of Panic Disorder: Predictors of Clinical Outcomes

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Objective: To evaluate the predictors of clinical outcomes in the short-term treatment of panic disorder.

Methods: This was a pooled analysis of two 10-week flexible-dose studies and two 12-week fixed-dose studies, in which 1595 adult outpatients with DSM-IV panic disorder (with or without agoraphobia) were randomly assigned to treatment with venlafaxine extended release (XR) 75, 150, or 225 mg/day or placebo. Predictors included panic severity (full-symptom panic attack frequency <8 or ≥8 panic attacks during each 2 week period in the 4 weeks prior to baseline) and gender. Other predictors included Panic Disorder Severity Scale (PDSS) score; and scores for CGI-I and CGI-S; HAM-A total, somatic, and psychic anxiety; HAM-D$_{17}$ total and depressed mood item; and Phobia Scale fear, avoidance, and overall phobia state. The primary efficacy measure was the proportion of patients free of full-symptom panic attacks.

Results: Among patients treated with venlafaxine XR, a significantly (P<0.05) higher proportion in the low severity group (69%) than in the high severity group (51%) and a significantly higher proportion of men (65%) than women (57%) were panic-free at endpoint. Also, among patients treated with placebo, a significantly higher proportion in the low severity group (53%) than in the high severity group (32%) and a significantly higher proportion of men (50%) than women (40%) were panic-free at endpoint. For nearly all baseline and endpoint clinical ratings, greater mean severity was associated with lower proportions of panic-free patients, in both treatment groups.

Conclusions: Gender and baseline panic disorder severity, and most baseline and endpoint clinical ratings, predicted panic-free status at endpoint.

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Rater Competency Improves Signal Detection

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Background: One source of noise affecting signal detection in CNS clinical trials is the inexperienced rater. Recent studies have shown that 20-60% of potential raters have had no previous experience with the selected primary CNS rating instrument, and that these inexperienced raters produce significantly greater scoring variance when compared to raters with more training experience. The present study examined the effect of rater competency on signal detection in the serial assessment of anxiety disorder.

Methods: More than 100 raters from clinical trial sites throughout the United States were asked to participate in a research study to evaluate sensitivity to change in anxiety ratings during a clinical trial. Sixty consenting raters were stratified into two groups based upon their previous participation in rater training programs conducted by UBC United BioSource Corporation, (formerly PharmaStar), an independent training company: Group A raters had attended four or more rater training programs at investigator meetings conducted by UBC; Group B raters were participating in their first UBC program. Raters observed eight videotaped interviews utilizing the Hamilton Rating Scale for Anxiety (Ham-A). The interviews showed two separate patient scenarios, each involving four sequential clinical trial visits. In addition, raters scored the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I). ANOVA was used to assess inter-rater variability for both groups of raters.

Results: The first patient revealed much improvement (CGI-I = 2) during the four sequential interviews with corresponding improvement on the Ham-A scores, whereas the second patient had essentially no change in clinical status during the four interviews (CGI-I = 4) with fluctuating scores on the Ham-A. Individual item deviations from acceptable scores were analyzed for each rater. Group A raters (more training experience) had significantly fewer item deviations and detected the clinical differences with significantly lower inter-rater variability than the Group B raters (less experienced). The raters with more training experience detected clinical change when it was present and differentiated between responders and non-responders.

Conclusions: In this study, more competent raters achieved better signal detection than inexperienced raters. Inexperienced raters are often unfamiliar with the administrative procedures and scoring conventions that seek to standardize the relatively subjective scoring instruments used in CNS trials. Clearly, more stringent standards for rater eligibility and required training programs for novice raters are necessary.

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Seizure, Suicide, and Mortality Risk Among Psychiatric Patients Based on FDA SBA Reports

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Background: Rare serious adverse events such as onset of seizures, suicide, suicide attempts, or mortality are a major concern when evaluating drug safety. The FDA generates a Summary Basis of Approval (SBA) dossier on each New Drug Application which details safety data on serious adverse advents.

Methods: We reviewed the SBA reports for 13 antidepressants, six antipsychotics, and three anxiolytics in order to assess seizure, suicide, and mortality risk among 110,960 psychiatric patients participating in phase II and phase III clinical trials. We conducted chi-square analysis to evaluate differences in risk rates based on gross numbers as well as person exposure years (PEY) data for patients assigned to either a psychotropic or placebo.

Results: The seizure risk was 10 times greater among patients with a psychiatric disorder compared to community non-patient samples. Some psychotropics (clozapine, clomipramine, bupropion IR, and alprazolam) appear to significantly increase seizure risk, whereas newer antidepressants (SSRIs and SNRIs) appear to significantly decrease seizure risk.

We did not detect any significant difference in suicide risk (suicide attempts and completed suicides) between depressed patients assigned to an antidepressant and those assigned to placebo. An analysis of three different databases indicated a 10-fold variability in suicide risk among the various antidepressant studies. A similar pattern emerged among two different databases for patients with schizophrenia.

PEY analysis for mortality rates among patients with schizophrenia indicated a significantly lower mortality rate among patients treated with an antipsychotic (atypical and typical) compared to patients assigned to placebo. Although not at significant level, the mortality rate was lower in patients assigned to an antidepressant compared to patients assigned to placebo. Conversely, patients treated with an anxiolytic had statistically higher mortality rates than those assigned to placebo. This finding was exclusively due to zero reported deaths for patients assigned to placebo.

Conclusions: These findings suggest that monitoring and interpreting serious, but rare adverse events is difficult and complicated. Interestingly, psychiatric diagnosis appears to play a significant role in the frequency as well as outcomes of these adverse events and possible effects of psychotropics. Some psychotropics with specific indications may have a deleterious effect, whereas other psychotropics may have beneficial effects. Other psychotropics appear to have no detectable effects. Thus, evaluations need to include appropriate drug indications, adequate sample sizes, and specific techniques for data analysis.

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Effect of Magnetic Stimulation on Cell Behavior

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Background: Magnetic stimulation (MS) has attracted a large amount of attention for the clinical effect in the treatment of different neurological and psychiatric disorders in the last decade. The explored modules for clinical purpose include repetitive transcranial magnetic stimulation (rTMS). The biological mechanism of its effect, however, has not been well studied. There are a few publications on genetic and neurotransmitter effects via animal studies. No available study was found using cell culture to directly study the MS effect on cell behaviors in vitro. We are reporting a preliminary study of low-frequency repetitive magnetic stimulation (rMS) effect on the behaviors of the PC12 cell, a clone of pheochromocytoma cell used as a cell model for neural diseases. This is part of an ongoing cooperative project with a research team in China.

Methods: In a 2 X 4 design, PC12 cells were divided into two main treatment arms, rMS only and rMS combined with nerve growth factor (NGF). In each arm, there were three rMS treatment intensities plus 0 as the control group: 0.38T, 1.14T, and 1.9T. A total of 10 stimuli at a frequency of 1Hz were applied to the cells for about 10 seconds each day and the treatment continued for a total of 9 days. The proliferation and neurite extension of PC12 cells were observed via inverse microscopy every day. Dopamine (DA) level in the culture medium was measured on the 3rd, 6th, and 9th days of treatment.

Results: The 1Hz rMS significantly facilitated the enation of neurite on PC12 cells at three rMS intensities. The amplitude of effect seemed dependent on magnetic intensity: the groups under 1.14T and 1.9T rMS treatment were significantly more likely to grow neurite than the 0.38T group. The extracellular DA levels yielded significant increase in the group under 0.38T stimulation, but tended to decrease in the higher intensity groups during the observed period. NGF displays different effects on observed cell behaviors. Overall, it facilitated the enation of neurite, but decreased the DA level. In combination, rMS plus NGF produced an augmentation effect at 0.38T and 1.14T, but deduction effect at 1.9T for the enation of neurite and varied effects on DA level.

Conclusions: Low-frequency 1Hz rMS to the PC12 cells might facilitate cell differentiation and influence the DA secretion. The results suggested that the effects and the amplitudes of these effects may be associated with the intensity of magnetic stimulation. The combination of rMS and NGF may produce different effects depending on the intensity of the stimulation. This suggests that the interaction of rMS with biological and pharmacological factors warrant further investigation at different levels for better understanding the mechanism of MS effects. This model also set up a novel convenient in vitro method to study genetic effects of MS at cell level with fewer ethical concerns than using animal and human subjects.

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Pharmacokinetics and Safety of Desvenlafaxine Succinate Extended Release: Effects of Chronic Hepatic Impairment

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Background: This study assessed the pharmacokinetics (PK) of desvenlafaxine succinate (DVS) in subjects with chronic hepatic impairment and matched healthy adults following administration of DVS extended release.

Methods: Twenty-four hepatically impaired (8 Child-Pugh class A, 8 Child-Pugh class B, and 8 Child-Pugh class C) adult subjects and 12 matched healthy adult (i.e., aged 18 to 65 years) subjects received single 100-mg oral doses of DVS. Blood and urine samples were obtained over 96 hours and analyzed. A model-independent method was used to derive single-dose PK parameters of DVS from plasma concentration vs time data. Statistical comparisons were made among groups using a 1-factor analysis of variance (ANOVA). Safety was evaluated based on reports of adverse events (AEs), physical examination, vital signs, and laboratory assessments.

Results: There were no statistically significant differences (i.e., >50%) for C_{max}, AUC_T, AUC to infinity (AUC_{INF}) or CL/F of DVS between hepatically impaired (Child-Pugh class A, B, or C) and healthy subjects. The median T_{max} of DVS ranged from 6 to 9 hours and was similar for all groups. Trends were observed for increased exposure in subjects with moderate to severe (i.e., Child-Pugh class B or C) hepatic impairment. The mean C_{max} of DVS in hepatically impaired subjects was up to 25% higher than in healthy subjects. Mean AUC_{INF}, CL/F, and $t_{1/2}$ of DVS were similar for subjects with Child-Pugh class A hepatic impairment and healthy subjects. In subjects with Child-Pugh class B or C hepatic impairment, there was a higher mean AUC_{INF}, (41% and 45%, respectively), lower clearance (12% and 25%, respectively), and longer $t_{1/2}$ (35% and 40%, respectively) compared with healthy subjects. The most common treatment-emergent AEs were nausea (reported by two healthy and three hepatically impaired subjects) and vomiting (reported by one healthy and two hepatically impaired subjects). There were no severe AEs.

Conclusions: Administration of single doses of DVS was safe and well tolerated in healthy and hepatically impaired subjects. Moderate to severe hepatic impairment may alter the PK of DVS.

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Escitalopram for Bereavement-Related Depression: A Pilot Study

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Background: Grief is a painful state that resembles major depression. Depression following loss is often left untreated because of the misconception that the symptoms are best attributed to grief and will remit spontaneously. Some even think treatment could impede grief work. A case series of bupropion in depressed bereaved patients found good depression response, with a small, though statistically significant improvement in grief. We conducted a small pilot study to investigate the effects of escitalopram on depression and grief.

Method: Twelve patients who met criteria for major depression 3-6 months following bereavement were recruited to participate in 12 weeks of open medication treatment. Participants underwent a baseline assessment and received escitalopram 10 mg/day, with an option to increase the dose to 20 mg, at week 4. Patients completed self-report rating scales (Beck depression inventory [BDI] and Inventory of Complicated Grief [ICG]) at treatment visits. An independent rater obtained Hamilton Depression scores at baseline and monthly thereafter.

Results: Eight patients completed the 12 week protocol. One dropped out because she did not like the depression diagnosis, one was discouraged by the results, and two for unknown reasons. Table 1 shows both ITT and completer analyses. There were large effect size changes for both depression and grief scales for both ITT and completers. Four patients (33% of ITT; 50% of completers) had remission of depression (Ham D < 7). Compared to a study of escitalopram for patients with complicated grief, who were seen more than 6 months post-loss, the patients in the current study had similar baseline ICG scores and greater reduction with treatment. Drop-out rate was also lower for the patients treated sooner after their loss.

Table 1: Treatment Outcome
Intent to treat

Variable	Pre treatment	Post treatment	Difference	Effect size
ICG	40.5 (13.0)	23.2 (18.2)	-17.3 (11.3)	1.53
BDI	25.5 (10.7)	10.4 (10.2)	-15.1 (8.7)	1.74

Completers

ICG	37.5 (11.4)	17.6 (12.9)	-18.7 (10.0)	1.86
HAM D	28.8 (5.6)	8.6 (5.3)	-20.1 (7.4)	2.72
BDI	22.3 (9.4)	5.3 (3.0)	-17.0 (8.7)	1.95

Conclusions: This open-case series shows promising results for escitalopram in the treatment of bereavement-related depression. Treatment also appears to be promising for grief symptoms. Better, rather than worse, response is seen for grief in the first 6 months after the loss.

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A New Scale for Evaluating Rater Interviewing Competency

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Background: Clinical experience, interviewing skills, and expertise administering rating instruments are essential components that impact rater ability to detect a treatment signal. While observation of videotapes is an effective method to evaluate rater scoring competency, a similar agreed-upon methodology to evaluate rater interviewing competency does not exist. This report describes a new tool developed by United BioSource Corporation to assess interviewing competency.

Method: Thirty taped interviews utilizing the Hamilton Rating Scale for Depression (Ham-D) and Hamilton Rating Scale for Anxiety (Ham-A) conducted by raters with varying research experience were reviewed by an expert consensus panel (ECP). ECP members categorized the interviews into four levels of competency: superlative, good, acceptable, and unacceptable. Additionally, each patient interview was scored by the rater conducting the interview and by the ECP members.

Following ECP review of the taped interviews, a group of five experienced clinician evaluators blindly reviewed and scored the interviews using the Research Interview Skills Assessment (RISA) Scale in a random order on two occasions separated by four weeks. Intra-Evaluator Agreement was assessed for each clinician evaluator and each of the five RISA scale domains using Kappa, and for the total RISA score using both Kappa and Intra-Class Correlation (ICC). Inter-Evaluator Agreement was assessed for each domain using Kappa, and for overall scores using Kappa and ICC. Additionally, the relationship between clinician evaluator scores was compared to the category assignments reported by the ECP for the 30 taped interviews. An Analysis of Variance (ANOVA) was conducted on the Ham-D and Ham-A item scores to assess the effect of interviewing competency on inter-rater variability. Subsequently, Kappa was calculated for the four interviewing categories of raters to assess whether interviewing competency yields higher inter-rater agreement.

Results: High Kappa and ICC values were seen for both Intra-Evaluator and Inter-Evaluator analysis for the RISA Scale, signifying that the scale is a valid and reliable tool for assessing interviewing competency. Higher Kappa scores were achieved by the "Superlative and Good" interviewers, which in turn correlated with higher inter-rater reliability for Ham-D and Ham-A item scores for these interviewers.

Conclusions: The RISA Scale was correlated with ECP scores and analysis of interviewing and scoring competency. Consequently, the scale was able to identify the "best" raters among a group of 30 raters. Interviewing competency is a critical component in determining overall rater competency to evaluate patients in CNS clinical trials.

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Documentary Evidence of Publication Bias in Pivotal Antidepressant Clinical Trials

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Background: Publication bias occurs when investigators, sponsors, journal reviewers, and/or editors tend to submit or accept manuscripts for publication based on the direction or strength of the study findings. When this occurs, it results in an incomplete and distorted perception of drug efficacy and safety. Most work on this topic has been based on-curiously-the published literature.

Methods: In this study, we examined the results from FDA reviews of drug companies' phase 2/3 clinical trial programs for 12 antidepressants approved since 1986. We compared the results from all study drug treatment arms (each tested against a placebo arm) to the corresponding results as published in journal articles. In order for a study to be considered to be positive for the purposes of this study, as with the FDA, the study drug must achieve statistical superiority over placebo (p <=.05) on the primary efficacy endpoint specified in the sponsor's original study protocol.

Results: The findings seemed to follow a rule of halves. Roughly half (51%) of the 89 study drug treatment arms were positive, while the other half were not significant (NS; studies either negative or failed). Of the 44 NS arms, somewhat more than half (60%) did not find their way into published form. (Our search included PubMed, the Cochrane Controlled Clinical Trials Register, and inquiries with the sponsors.)

Results on the remaining 18 NS arms were published. Of these, eight (44%) were acknowledged to be NS. The remaining 10 (56%) were published as positive (as judged by the finding highlighted in the abstract and the first figure), often using the result from a secondary or post hoc analysis.

Overall, as a result of publication bias, the percentage of positive treatment arms was increased from 51% (according to the FDA reviews) to 87% (according to the journal publications).

These data are categorized in this fashion for each of the 12 antidepressants. The data are also analyzed statistically to examine the effect of publication bias on the p values and the effect sizes.

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Comparative Effects of Ziprasidone and Olanzapine on Markers of Insulin Resistance: Results of a 6-Week Randomized Study in Patients with Acute Schizophrenia

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Background: Insulin resistance is highly prevalent in patients with schizophrenia, and individuals with insulin resistance in the upper tertile are at increased risk for developing cardiovascular disease. A serum triglyceride–to–high-density lipoprotein cholesterol (TG:HDL-C) ratio of >3 has emerged as a simple and useful marker of significant insulin resistance in nondiabetics, with 64% sensitivity for those in the upper tertile, while more-difficult-to-obtain fasting insulin levels carry only a 57% sensitivity.

Methods: Using data from a randomized, double-blind, 6-week trial, analysis of changes in TG:HDL-C ratio and serum insulin levels was performed for subjects treated with ziprasidone or olanzapine.

Results: At baseline, both drug cohorts had median TG:HDL-C ratios approaching 3 (ziprasidone, 2.67; olanzapine, 2.91). At study endpoint, there was a significant change in median TG:HDL-C ratio for the olanzapine-treated (0.60; P=0.0001), but not the ziprasidone- treated subjects (0.13; P=0.435). After adjustment for baseline differences, the increase in TG:HDL-C ratio was significantly greater for the patients randomized to olanzapine (P=0.006). The median change from baseline in insulin level was also significant for the olanzapine group (3.30 μU/mL; P<0.0001), but not the ziprasidone group (0.25 μU/mL; P=0.328).

Conclusions: In this short-term study, ziprasidone was not associated with change in the TG:HDL-C ratio, whereas olanzapine was associated with a significant increase in this parameter. Olanzapine, but not ziprasidone, also significantly increased insulin levels. These findings are consistent with the American Diabetes Association/American Psychiatric Association Consensus Statement regarding the greater risk for diabetes and hyperlipidemia during olanzapine treatment relative to ziprasidone.

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Session II - 80

Effectiveness of Aripiprazole Versus Standard-of-Care (Schizophrenia Trial of Aripiprazole: STAR Trial)

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Background: Naturalistic trials provide an opportunity to assess the overall performance of drugs using measures which encompass efficacy, safety, and tolerability (i.e. effectiveness). We compared the effectiveness of aripiprazole to standard of care after 26 weeks of treatment among community-treated patients with schizophrenia warranting a change in current medication due to tolerability problems and/or suboptimal clinical symptoms control.

Methods: A total of 555 patients were equally randomized to open-label treatment of aripiprazole (10-30 mg/day) or standard-of-care (SOC) (olanzapine 5 - 20 mg/day, or quetiapine 100 - 800 mg/day or risperidone 2 - 8 mg/day, with up to 16 mg/day). Clinicians were free to select the most appropriate SOC agent for the patient. Overall effectiveness was evaluated using the validated[1] Investigator Assessment Questionnaire (IAQ) Total Score at Week 26 (LOCF). The IAQ Total Score is the sum of 10 items: positive symptoms, negative symptoms, somnolence, weight gain, prolactin elevation, akathisia, EPS, cognition, energy, and mood. Lower scores correlate with better effectiveness. Validation studies also showed a correlation of the IAQ with CGI-I, preference of medication (POM), and unit decreases in IAQ score correlated with a 20% improvement in the risk of discontinuation. ANOVA was used for all comparisons.

Results: Mean IAQ Total Score at Week 26 was significantly better for aripiprazole (25.7 +/- 0.5) versus SOC (27.7 +/- 0.5 p<0.001). CGI-Improvement response ("very much improved" or "much improved") rate also was significantly higher for aripiprazole (44%) than for SOC (34%; p=.009). More patients in the aripiprazole group (47.4%) compared with SOC (28.6%) rated their study medication as "much better" than prior treatment at Week 26 (p<0.001) on the POM scale.

Conclusions: Aripiprazole demonstrated clinically superior effectiveness to SOC in the naturalistic setting of the STAR trial. In real-world practice, medication choices should consider efficacy, safety, and tolerability issues.

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Session II - 81

Efficacy of Ziprasidone in the Treatment of Schizoaffective Disorder: An Analysis of Two Fixed Dose, Placebo-Controlled Trials

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Background: Many clinical trials of atypical antipsychotic treatment include patients with both DSM-IV–defined schizophrenia and schizoaffective disorder. However, schizoaffective disorder lies between bipolar disorder and schizophrenia, phenomenologically and prognostically. Given the potentially independent course and outcome for patients with schizoaffective disorder, we sought to assess clinical response and to evaluate any dose-response relationship, in patients with schizoaffective disorder.

Methods: Analysis of hospitalized patients with schizoaffective disorder (n=96) was performed using pooled data from two similarly designed 6-week, fixed-dose, double-blind, placebo-controlled trials. Subjects were rapidly titrated (within 3 days) to their respective fixed doses. Efficacy (change in PANSS total and subscales, MADRS, and CGI-S) was assessed by ziprasidone dose group (40, 80, 120, and 160 mg/day). Dose response was assessed by a standard linear contrast analysis.

Results: Linear contrast analysis (excluding placebo) examining the PANSS total score showed a linear dose-response trend (p=0.05), with greatest improvement observed at the 160 mg/d dose. At 160 mg/d, significant improvement vs placebo (p<0.025) was observed for change in PANSS total, PANSS positive subscale, PANSS negative subscale, MADRS and CGI-S with effect sizes (Cohen's d) of 1.0, 1.2, 0.8, 0.5, and 1.1, respectively. Ziprasidone 160 mg/d was also superior to all lower doses combined (40, 80, and 120 mg/d) for PANSS total change (p=0.02).

Conclusions: Ziprasidone was associated with substantial improvement in psychotic as well as depressive symptoms, and was generally well-tolerated, in patients with schizoaffective disorder. A linear dose-response was noted, suggesting that rapid titration to 160 mg/d is associated with optimal treatment response.

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Effect of Regression to the Mean on the Assessment of Antipsychotic-Induced Weight Gain

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Background: Analyses of baseline and follow-up measurements taken in clinical studies are often confounded by intra-subject variability and changes not related to drug treatment. The principle of regression to the mean[1] (RTM) predicts that mean weight loss (or gain) will tend to occur in a group selected on the basis of high (or low) baseline values, even in the absence of real change.

Methods: To assess the effect of RTM on the determination of antipsychotic-induced weight change, we analyzed data from a randomized, double-blind, placebo-controlled one-year study of ziprasidone in patients with schizophrenia.[2] Patients were classified according to their baseline BMI: underweight (<18.5, N=8); normal (18.5-24.9, N=150); overweight (25-29.9, N=97); and obese (>30, N=39). Post-hoc regression analysis was performed to identify the RTM effect and to correct for this bias using data from the placebo-controlled group.

Results: The overall mean baseline weight was comparable for ziprasidone (157.5 lb, N=219) and placebo (159.9 lb, N=75) subjects. Linear regression analysis showed that the mean follow-up weight of high BMI (BMI >25) patients was lower than their baseline values in the ziprasidone arm, with the greatest weight loss, on average, in the highest BMI patients. Examination of the placebo results showed a similar weight loss trend in high BMI patients, demonstrating the effect of RTM on these repeated measurements. The mean weight change in the placebo group was -20.9 lb from a baseline weight of 202.6 lb in the obese group; -7.7 lb from 169.8 lb in the overweight group; and –5.1 lb from 147.6 lb in the normal BMI group. The placebo-corrected (subtracted) effect of ziprasidone on mean weight change was +2.2 lb and +2.9 lb, respectively, for normal and high BMI patients, after removing the bias due to RTM. There was no significant interaction between baseline BMI ranges and effect of ziprasidone treatment (p=0.216). Overall effect of ziprasidone (placebo-corrected) on weight change (+2.6 lb) was statistically non-significant (p=0.18, ANCOVA adjusted for baseline weight and time on study).

Conclusions: These results suggest that accurate assessment of antipsychotic-induced weight change in relation to baseline BMI requires correction for RTM. Previous reports on antipsychotic induced weight change have generally not corrected for the influence of RTM. This omission has likely resulted in a systematic underestimation of weight change associated with atypical antipsychotic treatment, particularly in patients with high BMI values.

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Weight Gain in Medicated First-Break Psychotic Patients and Medication-Free Controls

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Background: BMI of patients suffering from schizophrenia exceeds that of population estimates. Most study samples include a high proportion of patients with chronic schizophrenia. We propose to examine the extent of weight gain introduced after initiation of pharmacological treatment in drug-naïve first-episode psychotic patients, thereby limiting various confounding variables such as multiple past medication trials, history of partial adherence, or poor diet and a sedentary lifestyle associated with chronic mental illness.

Methods: Medication-free and medication-receiving first-episode psychotic subjects receiving antipsychotics along with medication-free age- and gender-comparable control subjects were observed over a 1 year time frame. Main outcome measure was the BMI difference. Exploratory data analysis was conducted to account for possible inter-individual and group differences. Proportions of patients and controls gaining a clinically significant 7% over baseline weight were calculated.

Results: The sample consisted of 96 first-break psychotic patient and 26 age- and gender-comparable healthy controls, all over 18 years of age. Patients on medication gained significantly more weight than healthy controls (p=0.013). Average time on meds did not differ (Oneway ANOVA, p $\leq$0.001). Younger patients (r=-0.246, p=0.016), patients with more negative symptoms at baseline (SANS global; r=0.212, p=0.039), and patients receiving atypical antipsychotics (p$\leq$0.001) gained more weight.

1 Year Changes	BMI Increase	%Change	>7% Wt Gain
Pts w/Antipsychotics			
Haloperidol (n=24)	1.3±1.8	5.2±7.5	
Risperidone (n=37)	2.3±3	9.9±12.9	
Olanzapine (n=10)	5.1±4.1	21.8±17.1	
Perphenazine (n=10)	0.3±0.7	1.6±3.4	
Other Antipsychotics (n=8)	4.4±3.1	18.5±11.9	
w/o Antipsychotics			
Patients (n=7)	0.5±2.4	2.7±10.3	
Healthy Controls (n=26)	0.3±1.5	1.0±5.5	
	p$\leq$0.001	*P$\leq$0.001*	

P=0.001, all Oneway ANOVA
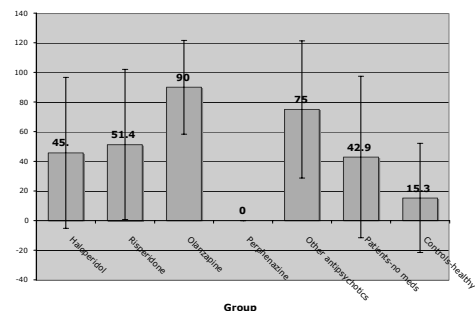
Conclusions: A high proportion of patients gained more than 7% over baseline weight. Differential contributions of the various antipsychotics prescribed were observed. Long-term metabolic side-effects are numerous and may proportionally increase with BMI. The first treatment intervention in drug-naïve patients is a critical step that has the potential to influence the course and outcome of what could become a lifelong illness. Tolerability is an important predictor of treatment adherence. Incorporation of these findings into treatment consideration appears useful.

Session II - 84

No Association of HOMA-IR with Diabetes and Obesity in Middle Aged and Elderly Patients with Schizophrenia

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Background: A number of reports have linked atypical antipsychotics with diabetes mellitus (DM), weight gain, and metabolic syndrome in schizophrenia patients in recent years. Though the causative mechanisms responsible for this linkage are unclear, some studies have suggested that increased insulin resistance (IR) might be the mechanism leading to these metabolic changes. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) has been widely used to assess IR in the general population, and this test has been recommended for examining the IR-related metabolic change in schizophrenia patients on atypical antipsychotics. However, few studies have examined the validity of HOMA-IR in schizophrenia.

Methods: We analyzed data from 103 patients over age 40 who were enrolled in our studies of antipsychotic-related metabolic changes. All the patients met DSM-IV criteria for schizophrenia and were taking antipsychotics. A diagnosis of DM was assigned based on medical chart review and a record of taking anti-diabetic medications (DM=73, Non-DM=30). Body Mass Index (BMI) was calculated based on height and weight measure (mean BMI=33.4, SD=6.7). The lab assessment included fasting glucose, insulin, and lipid panel. HOMA-IR was calculated with standard formula.

Results: The DM and non-DM groups did not differ in age, gender, education, and ethnicity. DM patients had significantly greater fasting glucose (150 vs. 111 mg, t=6.48, df. 97, p<. 02) and increased BMI (33 vs 28, t=5.16 df. 85, p<.05), but significantly lower fasting insulin (33 vs 51 units, t=4.6, df.97, p<.05) compared to those without DM. There was no significant difference in HOMA-IR between DM and Non-DM groups. There was no significant correlation between HOMA-IR and BMI (r=.032, p=.79).

Conclusions: Diabetes and obesity in schizophrenia patients were not associated with IR changes measured by HOMA-IR. This may be due either to less sensitivity of HOMA-IR measure itself or to mechanisms other than increasing insulin resistance in schizophrenia patients with DM or obesity.

Session II - 85

Reliability and Validity of a Computerized Neurocognitive Test for Research in Schizophrenia

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Background: Neurocognitive testing has been proposed as a way to measure schizophrenic patients' clinical state, as an indicator of the course of the disorder, and as a guide to treatment choices. It has been suggested that an appropriate battery for schizophrenia trials should include tests of seven domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The computerized test battery CNS Vital Signs has been modified for clinical research in schizophrenia and bipolar disorder, and is currently used in clinical trials in 45 countries and in 54 languages.

Methods: Test-retest reliability of the modified battery (VS-M) was measured in 117 subjects tested on two occasions, separated by (on average) 42 days. The discriminant validity of the battery was evaluated in a naturalistic, cross-sectional study of 127 subjects.

Subjects: The TRT sample consisted of 117 Ss ranging in age from 7 years to 85. There were 40 normals and 77 patients with diverse neuropsychiatric disorders. The discriminant validity sample consisted of 32 treated patients with schizophrenia, 39 treated bipolar patients, and 56 normal controls, ranging in age from 18 to 62 years.

Results: All of the domain scores, and 29 of 35 primary scores, were significantly correlated on test-retest ($P < 0.05$), with correlation coefficients ranging from 0.51 to 1.00. Significant group differences were expressed in all cognitive domains. Compared to normal controls, schizophrenics perform poorly in every cognitive domain. Bipolar patients are also impaired, but not nearly so much as the schizophrenic patients.

Conclusions: The VS-M battery was clinically acceptable to a diverse group of neuropsychiatric patients, and generated scores that were reliable on test-retest. The VS-M battery successfully discriminated among schizophrenic patients, bipolar patients, and normal controls. Deficits in social acuity, executive control, and working memory appear to be the most pertinent to the schizophrenic classification. Attention and processing speed are also important, but not to the same degree. The superordinate cognitive abilities that mediate successful performance in all of these tests are effortful or complex attention, information processing speed, and the ability to organize one's response sets with flexibility and efficiency.

Session II - 86

Concomitant Psychotropic Medications in Treatment of Schizophrenic Patients: Baseline Use in the CATIE Trial

Miranda Chakos, M.D. [1], Ira Glick, M.D. [2], Alex Miller, M.D. [3], Del Miller, M.D. [4], Jay Patel, M.D. [5], Mark Hammer, M.D. [6], Robert Rosenheck, M.D. [7]

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Background: Due to an inadequate response of many patients with schizophrenia to antipsychotic treatment, clinicians struggled to find strategies to improve outcome by augmenting with so-called ancillary or concomitant psychotropic medications (CPMs). These included combining antipsychotics, or combining an antipsychotic with an antidepressant, mood stabilizer, anxiolytic agents, or sedatives. This strategy has not changed even with the introduction of second-generation agents (SGAs). In fact, polypharmacy has become the rule rather than the exception in the United States and elsewhere. This change has evolved despite (with few exceptions) an almost total lack of controlled scientific data supporting the practice.

Methods: CPMs and anticholinergic use was studied at baseline in a large diverse population of people with schizophrenia who participated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial. The central measures of interest were the total number of CPMs prescribed to each patient and use of each separate class of drugs. The prevalance and correlates of CPMs and anticholinergic use in schizophrenia was examined.

Results: The strongest predictors of being on more numbers of CPMs were being anxious or depressed, being female, and being treated with SGAs. Conversely, African-American subjects and those with better neurocognitive functioning were less likely to be on several CPMs. Antipsychotic polypharmacy and anticholinergic medications were associated with lower neurocognitive scores. In some cases, the presence of symptoms that were likely targets of the CPM, such as depression, remained prominent, suggesting only partial response.

Conclusions: Use of CPMs in treatment of schizophrenic patients is prevalent, despite little information with regards to efficacy and liabilities associated with these interventions. CPM use in the treatment of schizophrenia is associated with diverse factors, including age, race, gender, persistent depression, concurrent anxiety and depressive disorder diagnoses, severity of illness, functional impairment, and neurocognitive impairment.

Poster # II - 87 was not presented at the meeting.

Session II - 88

Assessment of Paliperidone Extended-Release Tablets, 6 mg, 9 mg, and 12 mg, in the Treatment of Acute Schizophrenia

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Background: Efficacy, safety, effect on patient personal, and social functioning and quality of sleep of paliperidone extended-release (paliperidone ER) tablets, an investigational psychotropic, were assessed in patients with acute schizophrenia.

Methods: This international, double-blind, parallel-group, placebo-controlled 6-week study randomized patients (n=630, age ≥18 years, PANSS total score 70-120) to receive paliperidone ER 6mg, 9mg, or 12mg, placebo, or olanzapine 10mg daily. This study was powered to assess the efficacy of paliperidone ER vs. placebo. Olanzapine was included for assay sensitivity only.

Results: Mean (SD) age in the ITT population (n=628) was 37.1±10.9 and 66% of patients completed the study. At endpoint, significant improvements in the primary efficacy measure (change in PANSS total score) were observed for all paliperidone ER groups (p<0.001) compared with placebo, and in all Marder PANSS factor scores (p<0.001). Patient functioning, assessed using the Personal and Social Performance scale, significantly improved at endpoint for paliperidone ER vs. placebo (6mg=9.1±15.5, 9mg=8.1±14.5, 12mg=11.5±16.0, placebo=0.5±15.5; p<0.001). Quality of sleep, as assessed by mean change at endpoint on a patient-rated Visual Analog Scale (VAS), was significantly improved for each paliperidone ER group vs. placebo: 6mg=13.5±33.8, 9mg=10.5±31.2, 12mg=12.2±32.5, placebo=1.0±35.5; p<0.001. There was no statistically significant difference in change in daytime drowsiness VAS score for paliperidone ER vs. placebo at endpoint. TEAE occurring >3% more frequently than with placebo were tachycardia; extrapyramidal disorder and hyperkinesia (paliperidone ER); and somnolence, tachycardia, and postural hypotension (olanzapine). EPS-related AEs were comparable for paliperidone ER 6mg, olanzapine, and placebo, but increased with paliperidone ER 9mg and 12mg. SAE frequency was similar among paliperidone ER (3%), olanzapine (2%), and placebo (2%).

Conclusions: In this study of patients with acute schizophrenia, paliperidone ER 6mg, 9mg, and 12mg were effective, well tolerated, and associated with improvements in personal and social functioning and quality of sleep, without producing or exacerbating daytime drowsiness.

Session II - 89

Vulnerability, Resilience, and Response to Psychotropic Drugs: Shared Genetic Factors?

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Background: An increasing number of studies suggests that etiological differences between major psychiatric disorders might be of a quantitative rather than qualitative nature. In fact, bipolar illness occurs at increased rates in families with schizophrenia, as schizophrenia occurs at increased rates in families with bipolar illness. A similar picture is observed with schizoaffective disorder, and overlaps with unipolar depression exist as well.

Methods: Based on data from 71 multiplex nuclear families (527 subjects) ascertained through an index case diagnosed with bipolar illness or schizophrenia, we have addressed the question of diagnosis-independent susceptibility to functional psychoses. Subjects were genotyped for 553 polymorphisms of a genome scan, along with 48 candidate genes hypothesized to be involved in psychotropic drug response. Our search for vulnerability loci included standard multipoint linkage analysis (Allegro) along with the multivariate genetic vector space method, which allows one to detect oligogenic configurations of genomic loci and their nonlinear interactions.

Results: Carried out separately for the two populations of families (bipolar versus schizophrenia index case), linkage analyses yielded several genomic regions on chromosomes 1, 4, 5, 6, 11, and 22, with striking similarities between NPL scores. The genetic vector space based analyses revealed both positive and negative genotype-phenotype correlations, thus suggesting the existence of co-existing vulnerability and resilience factors. Most interestingly, there was some overlap with genomic regions identified through our study on psychotropic drug response (257 patients treated with antidepressants or antipsychotics and genotyped for 178 candidate genes), where positive as well as negative correlations likewise suggested the existence of mechanisms that can support or impede recovery. No single genomic locus seemed to be either necessary or sufficient for having the phenotype or to explain more than just a small percentage of observed phenotypic variance, whereas significant nonlinear interactions between the genomic loci appeared to play a key role and exceeded main effects by far.

Conclusions: Evidence from two combined molecular-genetic studies including 784 genotyped subjects clearly supports a strong biological relationship between vulnerability to major psychiatric disorders and recovery under psychotropic drug treatment. Shared genetic factors can increase or decrease the likelihood for developing the disorder, as they can support or impede recovery. Detailing the characteristics of these factors will ultimately lead to considerably improved treatments along with a more personalized medicine.

Session II - 90

Higher Serum Insulin Level Is Associated with a Better Psychopathology Profile in Acutely Ill Non-Diabetic Inpatients with Schizophrenia

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Objective: Recent studies have suggested a beneficial role of insulin on brain function and psychological well-being. This study was undertaken to examine whether fasting serum insulin levels are associated with the psychopathology profile in a cross-sectional sample of acutely ill non-diabetic inpatients with schizophrenia.

Methods: Subjects were recruited from a county hospital. Each subject underwent a psychopathology assessment with the Positive and Negative Syndrome Scale (PANSS). A fasting blood sample was taken to measure serum insulin, plasma glucose, and lipids.

Results: Twenty-six subjects (7 females, 19 males) were included in the study. Pearson correlation analysis showed significant inverse relationships between serum insulin level and PANSS-Total, Positive Symptom subscale, and General Psychopathology subscale scores (r = -0.41, p = 0.037; r = -0.49, p = 0.010; r = -0.45, p = 0.023, respectively). However, there was no significant relationship between serum insulin level and PANSS-Negative Symptom subscale score (r = -0.13, p = 0.53). Partial correlation analysis showed that the inverse relationships between serum insulin level and PANSS-Total, Positive Symptom subscale, and General Psychopathology subscale scores became even stronger after controlling for potential confounding variables including gender, family history of mental illness, and age of illness onset.

Conclusions: Higher serum insulin levels are associated with a better psychopathology profile in acutely ill non-diabetic inpatients with schizophrenia. It is speculated that insulin might improve clinical symptoms of schizophrenia by interacting with dopamine and other neurotransmitter systems.

Session II - 91

Ginkgo Biloba Extract and Its Effect in Patients with Schizophrenia

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Background: A number of studies suggest that gingko biloba extract (GBE) may have a beneficial effect on cognitive function. Earlier, we conducted a preliminary open-label study, which suggested that patients with schizophrenia may show improvement in some aspects of their cognitive performance after GBE was added to their medication. Since many patients with schizophrenia exhibit significant cognitive impairment, we conducted a study to determine whether GBE may improve patients' cognitive performance.

Methods: We conducted a double-blind placebo-controlled study of GBE added to the ongoing medication of stable patients with schizophrenia or schizoaffective disorder. We enrolled 52 subjects. The aim of the study was to determine whether patients' psychiatric and cognitive symptoms improved on GBE. Patients had a series of cognitive and psychiatric assessments before and throughout the 12-week study. We divided the cognitive tests in tests of frontal function, executive and working memory, semantic (similarities and verbal fluency), and visual memory (recall of faces). Some patients (19) agreed to participate in an evoked potential study to examine whether GBE-induced changes were captured through electrophysiological findings.

Results: GBE was well tolerated. The GBE group, however, did not show any significant difference compared to the placebo group in any of the variables examined: psychiatric symptoms, cognitive performance, and neuroleptic-induced movements disorder symptoms (such as tardive dyskinesia or extrapyramidal symptoms). In addition, GBE produced no changes in the evoked potential studies. Since some reports suggested that GBE may be associated with increased risk for spontaneous bleeding, we assessed the effect of GBE on bleeding time. GBE did not affect the bleeding time in our patients.

Conclusions: Our study failed to suggest that GBE has any therapeutic effect in patients with schizophrenia. There were no detected effects on the psychiatric symptoms, cognitive performance, or medication-induced movement disorder measures. In addition, GBE produced no significant electrophysiological changes.

Session II - 92

Relationship Between Improvements in Negative Symptoms and Functioning After Accounting for Changes in Positive Symptoms

Dawn Velligan, Ph.D. [1], Mei Wang, M.S. [1], George Haig, Pharm.D., M.B.A. [2], Scott Lancaster, M.S. [2], Thomas Taylor, Ph.D. [3], Larry Alphs, M.D., Ph.D. [2]

[1]University of Texas, San Antonio, [2]Pfizer Global Research and Development, Ann Arbor, MI, [3]Pfizer Global Research and Development, New York, NY

Background: Improvements in the positive symptoms of schizophrenia are generally easily discernible, and long-term improvements have resulted in higher levels of functioning. Improvements in negative symptoms often are more subtle. We previously demonstrated that changes in negative symptoms are significantly and strongly correlated with changes in functioning. The purpose of this analysis was to determine whether changes in negative symptoms are associated with changes in functioning after adjusting for the effects of positive symptoms.

Methods: Stable outpatients with schizophrenia or schizoaffective disorder participating in one of three medication or psychosocial treatment intervention studies were assessed at baseline and 9 months using the Negative Symptom Assessment-16 (NSA-16; n=96), the Brief Psychiatric Rating Scale (BPRS; n=97), the Quality of Life Scale (QLS; n=99), the Multnomah Community Ability Scale (MCAS; n=96), the Global Assessment of Functioning (GAF; n=95), the Social and Occupational Functioning Assessment Scale (SOFAS; n=96), the Frontal Systems Behavioral Scale (FrSBe; n=74), the Functional Needs Assessment (FNA; n=95), and the Life Skills Profile (LSP; n=95). A positive symptom factor was composed of items on the BPRS assessing unusual thought content, hallucinations, and conceptual disorganization. Change scores were calculated by subtracting baseline scores from the scores at 9 months. Statistical significance was calculated by change in the log likelihood of two nested models, the first containing the BPRS positive symptoms score as the independent variable and the second containing both BPRS positive symptoms and NSA-16 scores.

Results: After accounting for changes in positive symptoms, negative symptoms were strongly and significantly associated with changes in functional outcome **(Table 1)**.

Table 1. Relationship Between Change in Negative Symptoms and Functional Outcomes

	Structured		Global		Performance Based		
	QLS	MCAS	GAF	SOFAS	FrSBe	FNA	LSP
Expected change in function score given a 5-point decrease in NSA-16 score	2.93	1.08	3.02	3.03	–3.73	3.33	1.40
P (association with NSA-16 after accounting for positive symptom changes)	0.0002	0.0339	<0.0001	<0.0001	0.0011	0.1003	0.0086

Conclusions: Improvements in negative symptoms are strongly associated with improvements in functioning after accounting for improvements in positive symptoms. The effects are strongest and most significant with the QLS and the global measures of function (GAF and SOFAS). Our analysis suggests that improving negative symptoms is important in decreasing the significant functional disability associated with schizophrenia.

Session II - 93

A Data-Driven Approach to Characterizing the Stages of Schizophrenia

Colette Kosik-Gonzalez, M.A. [1], Stephen Rodriguez, M.S. [1], Cynthia Bossie, Ph.D. [1], Mary Kujawa, M.D. [1], Georges M. Gharabawi, M.D. [1], John Docherty, M.D. [2]

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Background: Although criteria exist for the diagnosis of schizophrenia, there is a need to more effectively communicate disease course to patients and families. Defining or characterizing the stages of schizophrenia may advance care by assessing treatment progress; identifying barriers to improvements; enhancing communication and setting expectations for patients, families, and caregivers; and identifying stage-specific aspects of treatment efficacy for targeting interventions.

Methods: A working group identified five domains for consideration in defining the stages of schizophrenia: symptom severity, function, cognition, stress tolerance, and physical health. Data from three studies were used to characterize patients with schizophrenia in different stages of disease. Study 1 was a double-blind, international, 6-week study of subjects with a recent acute exacerbation (n=382). Studies 2 (n=323) and 3 (n=725) were international, one-year studies in symptomatically stable adults with chronic disease. Measures of symptomatology (Positive and Negative Syndrome Scale [PANSS]), function (Personal and Social Performance [PSP] and Strauss-Carpenter Level of Function [LOF] scales), and overall clinical status (Clinical Global Impressions-Severity [CGI-S]) were employed. These data served as basis for development of an interactive tool designed to provide physicians with a mechanism for staging patients within the course of remission. This tool will help profile patients with respect to the various domains, and track patients through treatment. Supportive materials specific to the needs of patients in each stage will be provided.

Results: Three patient groups were identified as Acute, Stable, and Remitted; they were characterized by distinct symptom profiles. Mean PANSS item scores were similar at baseline for the two populations of stable patients and differed from those of both acute and remitted patients. Mean CGI scores were 5.4 in acute patients, 3.6 in stable patients, and 2.7 in remitted patients. Mean Insight scores (PANSS G12) were 3.8 in acute patients, 2.6 in stable patients, and 2.0 in remitted patients. There were some differences in most LOF items, with overall higher mean scores in the remitted group. The percentage of patients with good functioning (PSP total, 71-100) was 27.6% in stable patients and 40.5% in remitters.

Conclusions: These data will guide the characterization of the stages of schizophrenia and the development of an innovative communication tool. In addition to evaluating distinct symptom profiles, this tool provides a unique resource for the long-term tracking of patient status in multiple domains, including symptom severity, function, cognition, stress tolerance, and physical health.

Poster # II - 94 was not presented at the meeting.

Session II - 95

Are Changes in Functional Outcomes Associated with Changes in Negative Symptom Factor Scores?

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Background: The Negative Symptom Assessment (NSA-16) scale is a 16-item clinician-rated instrument to assess the negative symptoms of schizophrenia. The NSA-16 is a valid and reliable measure of negative symptoms with good rater training efficiency. Negative symptom factors represented in the NSA-16 include communication, affect, social activity, motivation, and motor retardation. We previously showed that improvements in NSA-16 scores are highly correlated with improvements in functioning, and that these correlations are stronger than correlations of positive symptoms with most functional measures. The purpose of this analysis was to determine which negative symptom factors within the NSA-16 structure are most highly correlated with measures of functioning.

Methods: Stable outpatients with schizophrenia or schizoaffective disorder participated in one of three medication or psychosocial treatment intervention studies. Baseline and 9-month assessments were completed for all patients on the NSA-16 (N=96), the Quality of Life Scale (QLS), the Multnomah Community Ability Scale (MCAS), the Global Assessment of Functioning (GAF), the Social and Occupational Functioning Assessment Scale (SOFAS), the Frontal Systems Behavioral Scale (FrSBe), the Functional Needs Assessment (FNA), and the Life Skills Profile (LSP). Change scores were calculated by subtracting the baseline scores from the scores at 9 months. Associations were assessed using Pearson's correlation coefficients.

Results: Changes in the NSA-16 total score were significantly associated with changes in each functional scale (Table 1). Individual negative symptom factors showing the highest correlation with functional outcomes were motivation, communication, and affect. The GAF showed significant correlation with all of the negative symptom factors, whereas the FNA and LSP each showed association with only two factors.

Table 1. NSA-16 Factor–Functional Outcomes Correlations (Pearson Coefficients)

Factor	Structured		Global		Performance Based		Clinician Rated
	QLS (n=99)	MCAS (n=96)	GAF (n=95)	SOFAS (n=96)	FrSBe (n=74)	FNA (n=95)	LSP (n=95)
Communication	−0.170	−0.251*	−0.430§	−0.386§	0.442§	−0.211*	−0.279†
Affect	−0.225*	−0.179	−0.467§	−0.395§	0.332†	−0.248*	−0.139
Social activity	−0.296†	−0.234*	−0.248*	−0.196	0.102	−0.002	−0.075
Motivation	−0.434§	−0.226*	−0.380§	−0.446§	0.390‡	−0.190	−0.507§
Motor retardation	−0.272†	−0.260*	−0.224*	−0.233*	0.138	−0.171	−0.195
NSA-16 total score	−0.423§	−0.338	−0.521§	−0.497§	0.414‡	−0.231*	−0.367‡

*$P \leq 0.05$, †$P \leq 0.01$, ‡$P \leq 0.001$, §$P \leq 0.0001$.

Conclusions: Among the negative symptom factors represented on the NSA-16, those most strongly associated with changes in clinician-rated and performance-based functional outcome ratings are motivation, communication, and affect. This analysis suggests that interventions that yield improvements in these factors are more likely to lead to improvements in functioning.

Session II - 96

Mapping the Neurocognitive Deficit-Functional Disability Relationship Using Partially Ordered Classification Models

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Background: Neurocognitive (NC) deficits and disability are core features of schizophrenia. However, for new treatment approaches to successfully target functionally critical NC deficits, those specific cognitive operations that are responsible for a range of disability dimensions have to be identified. Yet, current statistical analysis methods for analyzing neuropsychological test data in schizophrenia are inherently insufficient for revealing valid cognitive impairment profiles, and hence for mapping NC-disability relationships. While neuropsychological tests aim to selectively sample discrete cognitive domains, most tests are polyfactorial, with performance often requiring several cognitive operations or "attributes." Conventional statistical approaches assign an individual test score of interest to a single attribute or "domain" (e.g. attention, executive) and composite scores are then calculated for each domain. This can yield misleading information about underlying cognitive impairments, as it is difficult to specify for which cognitive operation a subject having a low test score may have poor functionality.

Methods: We report findings applying a new method for examining neuropsychological test data in schizophrenia, based on finite partially ordered sets (posets) as classification models. We studied 220 patients having schizophrenia or schizoaffective disorders who were recently discharged from hospital and followed for up to 18 months. A baseline comprehensive NC test battery was analyzed using Bayesian statistical methods (yielding posets) to classify patients into discrete groupings, or "states," each having a unique cognitive profile.

Results: Twelve cognitive "classes" described the sample. Resulting classification models provided detailed "diagnoses" into "attribute-based" profiles of cognitive strength/weakness, mimicking expert clinician judgment. Classification was efficient, requiring few measures to achieve accurate classification. Attributes associated with these states (working memory, capacity for divergent thinking, cognitive flexibility, and psychomotor speed) were then associated with two domains of functional outcome (work/education and residential functioning) rated at follow up. Working memory was associated with work/education outcome but not residential outcome (e.g. independent living). On the other hand, the remaining three attributes were associated with residential but not work/education outcome after multiplicity correction.

Conclusions: Different neurocognitive operations may be responsible for different outcome domains. Poset methodology may offer a more reliable method, relative to other statistical approaches, of clarifying patterns of relationships between discrete neurocognitive attributes and domains of functional outcome.

Session II - 97

Sedative Effects of Transmucosal Zolpidem

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Background: Low-dose transmucosal zolpidem (TMZ) may serve as an effective treatment for middle-of-the-night insomnia since the sedative effects are expected to be rapid and short lived, not lasting more than 4 hours. The present study evaluated the pharmacokinetics (PK), pharmacodynamics (PD), safety, and dose-proportionality of TMZ in healthy adults following daytime sublingual administration of single doses of 1.0 mg, 1.75 mg, and 3.5 mg zolpidem tartrate lozenges.

Methods: Healthy adults (N=24, mean 37.6 yrs) in good medical health and without history or symptoms of sleep pathology were tested in this double-blind, placebo-controlled, 4-way crossover study of 2 consecutive days of morning dosing with placebo or with 1.0 mg, 1.75 mg, or 3.5 mg TMZ. On Day 1 of each period, PD endpoints consisting of DSST, SCT, CRT, Word Recall and Self-Rating of Sedation on VAS were evaluated at pre-dose, at 20 minutes, and at 1, 1.5, 2, 3, 4, and 5 hours post-dose. Repeated blood samples were drawn for PK analysis over 12 hours after dosing on Day 2.

Results: Significant reductions in DSST scores occurred after administration of TMZ 1.75 mg and 3.5 mg as early as 20 minutes and lasted for 1.5 hours post-dose (-6.6; p=0.0132 and -14.8; p<0.001). Relative to baseline ratings, significant increases in subjective sedation were reported for TMZ 1.75 mg and 3.5 mg up to 120 minutes post-dose (p=0237; p=0205). Self-rated VAS sedation scores began trending toward baseline levels for both the 1.75 mg and 3.5 mg doses between 180-240 minutes following drug administration. Other PD outcomes were qualitatively similar. TMZ 1.0 mg did not differentiate from placebo on any measure. Cmax and AUC for TMZ were dose-proportional; Tmax was 36.0, 37.9, and 37.9 minutes for 1.0 mg, 1.75 mg, and 3.5 mg TMZ, respectively. TMZ plasma levels higher than 20 ng/ml occurred between 15 and 240 minutes. All doses were well tolerated with no serious adverse experiences reported or observed.

Conclusions: Sedative effects of zolpidem occurred following sublingual administration at <50% the reported typical PO adult dose of 10 mg and at less than half of its reported Tmax. These data suggest that TMZ may produce a faster sleep onset and shorten duration of action, thereby making it appealing for PRN administration in response to symptoms of insomnia, including trouble re-initiating sleep in the middle of the night.

Session II - 98

Evaluation of Indiplon Pharmacokinetics and Drug-Drug Interactions

Brian W. Corrigan, Ph.D. [1], Ellie Hershberger, Ph.D. [1], Rahdi Abdulnabi, Ph.D. [1], Robert Abel, Ph.D. [1], Haig Bozigian, Ph.D. [2], Ta-Kung Chen, Ph.D. [2], Robert Farber, Ph.D. [2]

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Background: Indiplon, a GABA-A potentiating hypnotic, has been shown to be effective in both inducing and maintaining sleep in patients with chronic insomnia. In vitro studies show indiplon is metabolized partly by CYP3A4 and partly by carboxyesterases and is approximately 80% protein bound. Indiplon is not a P-glycoprotein substrate.

Methods: A series of studies in young, healthy volunteers evaluated the pharmacokinetic (PK) profile of indiplon and potential for clinically relevant pharmacokinetic (PK) interactions between indiplon (up to 30 mg dose) and agents with narrow therapeutic indices, several antidepressants, and an antipsychotic.

Results: Indiplon Cmax and AUC were dose-proportional across the studied dose range (5-30 mg). Peak plasma concentrations occurred within 1 hour of administration and the mean terminal elimination half-life was 1.5-2 hours. Indiplon did not alter the PK of warfarin, theophylline, or digoxin. The pharmacodynamic effects of warfarin 20 mg (PT, INR) were not altered by indiplon 30 mg. Co-administration of indiplon with antidepressants (sertraline 50 mg/day, paroxetine 20 mg/day, venlafaxine 150 mg/day, amitriptyline 50 mg/day) did not alter indiplon pharmacokinetics and there were no additive effects in tests of psychomotor function or alertness (Digit Symbol Substitution Test, sleepiness VAS). Co-administration of indiplon with olanzapine 5 mg had no effect on the PK of either agent. Indiplon exposure increased by approximately 2.4-fold when administered with the potent CYP3A4 inhibitor ketoconazole, and by approximately 25% when administered with the moderate CYP3A4 inhibitor erythromycin. Co-administration with the potent CYP3A4 inducer rifampin decreased indiplon exposure by approximately 70%. No tolerability concerns were identified in these studies.

Conclusions: Indiplon is rapidly absorbed, has a relatively short half-life, and a dose-proportional PK profile. No clinically relevant drug-drug interactions were observed in the presence of several antidepressants, an antipsychotic, and agents with narrow therapeutic indices. Clinically relevant changes in indiplon exposure were observed with potent CYP3A4 inhibition and induction, but not with modest CYP3A4 inhibition. No other clinically relevant interactions with inhibitors were observed. This profile supports the use of indiplon as a treatment for insomnia.

Session II - 99

Efficacy and Safety of Doxepin at 1 mg, 3 mg, and 6 mg Doses in Elderly Adults with Primary Insomnia

Thomas Roth, Ph.D. [1], Roberta Rogowski, B.S.N. [2], Steven Hull, M.D. [3], Martin Cohn, M.D. [4], Alan Lankford, Ph.D. [5], David Mayleben, Ph.D. [6], Martin Scharf, Ph.D. [7]

[1]Henry Ford Sleep Disorders Center, Detroit, MI, [2]Somaxon Pharmaceuticals, Inc, San Diego, CA, [3]Vince and Associates Clinical Research, Overland Park, KS, [4]Sleep Disorders Center of South West Florida, Naples, [5]Sleep Disorders Center of Georgia, Atlanta, [6]Community Research Management Associates, Cincinnati, OH, [7]Tri-State Sleep Disorders Center, Cincinnati, OH

Background: Previous research demonstrated that the sedative-hypnotic properties of doxepin are retained at low doses. This randomized, placebo-controlled, cross-over study evaluated the efficacy and safety of doxepin at 1 mg, 3 mg, and 6 mg doses in elderly adults with insomnia.

Methods: Randomized patients (n=76) reported ≥3 months of DSM-IV primary insomnia, and had ≥60 minutes of wake-time-during-sleep (WTDS), 240-410 minutes of total-sleep-time (TST), and ≥10 minutes of latency-to-persistent-sleep (LPS), confirmed by polysomnography (PSG). Patients received a random sequence of doxepin 1 mg, 3 mg, 6 mg, and placebo. Treatment periods consisted of two PSG assessment nights with a 5- or 12-day drug-free interval. Primary endpoint was WTDS; secondary endpoints included wake-after-sleep-onset (WASO), sleep efficiency (SE), LPS, and subjective sleep assessment.

Results: All three doxepin groups had dose-related significant improvements in WTDS ($p \leq 0.0001$), WASO ($p < 0.0001$), and overall SE ($p < 0.0001$) versus placebo. In the 6 mg dose-group, SE was significantly increased during all thirds-of-the-night ($p < 0.005$). SE was significantly increased in the 3 mg dose-group during the second and final thirds-of-the-night ($p < 0.005$). LPS was numerically reduced; subjective sleep latency was significantly reduced ($p = 0.017$) in the doxepin 6 mg dose-group. Other subjective efficacy results were consistent with PSG results. There were no significant group differences in next-day residual sedation, and sleep architecture was generally preserved. There were no adverse events occurring at an incidence >2% in the doxepin dose-groups; incidence of all events was comparable to placebo.

Conclusions: In elderly adults with insomnia, doxepin at 1 mg, 3 mg, and 6 mg doses was well-tolerated and produced dose-related significant improvement in PSG-defined and patient-reported sleep maintenance and duration endpoints that persisted through the final third-of-the-night with no reported anti-cholinergic effects or significant hangover/next-day residual effects. Effects on sleep onset were also observed at the highest doses. These data suggest that doxepin 1 mg, 3 mg, and 6 mg may improve sleep maintenance, sleep duration, and sleep onset in elderly adults with primary insomnia.

Session II - 100

Sleep Laboratory Assessment of Indiplon in Primary Insomnia: Results of a Double-Blind, Placebo-Controlled, Crossover Trial

Brian Klee, M.D. [1], Russell Rosenberg, Ph.D. [2], Yin Kean, M.P.H. [3], Robert Farber, Ph.D. [3]

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Introduction: To evaluate the efficacy of indiplon, a novel α_1 subunit-selective, $GABA_A$ receptor potentiator, in patients diagnosed with primary insomnia characterized by sleep maintenance difficulties.

Methods: Patients (N=100; mean age, 51 years, range, 22-78 years; female, 63%) who met DSM-IV criteria for primary insomnia, and who reported >60 minutes of wake time after sleep onset, were randomized to a double-blind, 2-period, 2-night crossover sleep lab comparison of indiplon 15mg and placebo. Polysomnographic (PSG) assessments included wake time during sleep (WTDS, primary outcome), wake time after sleep onset (WASO), latency to persistent sleep (LPS), total sleep time (TST), and patient-rated sleep quality. Next-day residual effects were evaluated using the Digit Symbol Substitution Test (DSST) and a 100-mm Visual Analog Scale (VAS) to assess daytime sleepiness. Comparisons were made using a crossover ANOVA model.

Results: Treatment with indiplon was associated with significantly reduced WTDS (60.4 ± 3.5 min vs. 71.5 ± 3.6 min; p=0.0036), reduced WASO (73.9 ± 4.0 min vs. 83.0 ± 4.0 min; p=0.0190), significantly shorter LPS (12.5 ± 1.1 min vs. 26.1 ± 2.4 min; p<0.0001), and significantly longer TST (389.8 ± 4.9 min vs. 362.8 ± 5.0 min; p<0.0001) relative to placebo. Sleep quality was rated as significantly improved on indiplon (3.3 ± 0.1) compared to placebo (4.0 ± 0.1; p<0.0001). The total incidence of any adverse events was not dissimilar on indiplon (8.0%) and placebo (10.4%). The mean pre-to-post-dose next-day residual change scores were not significantly different for the DSST ($+1.7 \pm 0.7$ vs. -1.0 ± 0.7; p=0.48) and the VAS (-0.2 ± 2.0 vs. $+0.4 \pm 2.0$; p=0.77).

Conclusions: The 15 mg dose of indiplon was safe and effective in inducing and maintaining sleep in patients with primary insomnia, as demonstrated by both objective PSG measures and subjective diary-based measures. Indiplon was well-tolerated, with no next-day residual effects.

Session II - 101

Symptom Response and Remission in Insomnia: Analysis of How Various Criteria Perform

Joanne Bell, Ph.D. [1], Karl Doghramji, M.D. [2], Robert Farber, Ph.D. [1]

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Objective: Response and remission are the two most commonly utilized measures of outcome in treatment studies of many psychiatric disorders (e.g., depression, anxiety), yet consensus regarding such criteria in the treatment of insomnia are lacking. The goal of this analysis was to test how various response and remission criteria for insomnia perform with respect to one another during the evaluation of the efficacy of a novel insomnia treatment, indiplon.

Methods: Month 1 efficacy data were analyzed from a prospective, double-blind, placebo-controlled trial utilizing indiplon 10 mg and 20 mg. Response and remission were evaluated using the following four outcome measures: (1) the 7-item Investigator Global Rating of Change (IGR-C); (2) the self-administered 7-item Insomnia Severity Index (ISI); (3) normative values for sleep onset and total sleep time from a community survey (Lichtstein et al, 2004); and (4) no longer meeting insomnia severity criteria required for study entry, consisting of latency to sleep onset >45 mins, wake time after sleep onset >45 mins, and total sleep time <330 mins.

Results: At Month 1, the two candidate responder criteria yielded the following response rates: IGR-C $\leq$2 (indiplon 10 mg, 45% vs. indiplon 20 mg, 58% vs. PBO, 23%), and ISI-total score $\leq$15 (indiplon 10 mg, 69% vs. indiplon 20 mg, 70% vs. PBO, 53%). At Month 1, the four remission criteria yielded the following remission rates: IGR-C=1 (indiplon 10 mg, 18% vs. indiplon 20 mg, 28% vs. PBO, 8%); ISI-total score $\leq$10 (indiplon 10 mg, 36% vs. indiplon 20 mg, 46% vs. PBO, 22%); return to community norm levels of sleep (indiplon 10 mg, 29% vs. indiplon 20 mg, 25% vs. PBO, 12%); and no longer meeting insomnia severity criteria for study entry (indiplon 10 mg, 32% vs. indiplon 20 mg, 33% vs. PBO, 17%).

Conclusions: Empirical data provide an important first step for establishing consensus clinical criteria for response and remission in the treatment of insomnia.

Session II - 102

Paliperidone Extended-Release 3 mg, 9 mg, and 15 mg Tablets: An International 6-Week Placebo-Controlled Trial in Schizophrenia

Michael Davidson, M.D. [1], Robin Emsley, M.D. [2], Michelle Kramer, M.D. [3], Lisa Ford, M.D. [3], Christiana Gassmann-Mayer, Ph.D. [3], Pilar Lim, Ph.D. [3], Guohua Pan, Ph.D. [3], Marielle Eerdekens, M.D. [4]

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Objective: Assessment of efficacy, safety, effect on personal and social functioning, and quality of sleep of investigational paliperidone extended-release (paliperidone ER) tablets in patients with acute schizophrenia.

Method: This double-blind, parallel-group, placebo-controlled study randomized patients (n=618, age ≥18 years, PANSS total score 70-120) to receive paliperidone ER 3 mg, 9 mg, or 15 mg, placebo, or olanzapine 10mg daily. The study was powered to assess efficacy of paliperidone ER vs. placebo. Olanzapine was included for assay sensitivity only.

Results: Significant improvements in the primary efficacy measure (change in PANSS total score) were observed at endpoint for all paliperidone ER groups (p<0.001) in the ITT set (n=605), and in all Marder PANSS factor scores (p≤0.005). Significant improvement from Day 4 (first observation point) was demonstrated for all paliperidone ER doses vs. placebo (p<0.05). Personal and Social Performance scale scores significantly improved at endpoint for paliperidone ER vs. placebo (3 mg=8.3±17.1, 9 mg=7.6±14.2, 12 mg=12.2±15.7, placebo=-1.5±15.8; p<0.001). Mean change at endpoint for quality of sleep, assessed by a patient-rated Visual Analog Scale (VAS), was improved for paliperidone ER vs. placebo: 3 mg=9.0±34.5 (p=0.059), 9 mg=12.3±34.9 (p=0.016), 15 mg=11.3±33.2 (p=0.075), placebo=3.6±36.0. There was no statistically significant difference in change in daytime drowsiness VAS score for paliperidone ER vs. placebo at endpoint. Incidence of EPS-related AEs was comparable for paliperidone ER 3 mg, olanzapine, and placebo, although higher with paliperidone ER 9 mg and 15 mg. SAE frequency was similar between paliperidone ER (7%), olanzapine (6%), and placebo (7%).

Conclusions: In this study, paliperidone ER 3 mg, 9 mg, and 15 mg were significantly effective in symptom control and were well tolerated, with improvements observed as early as Day 4 (first observation point) in patients with acute schizophrenia. The data suggest significant improvements in personal and social functioning with paliperidone ER without induction or exacerbation of daytime drowsiness.

Session II - 103

Dose-Response Analysis of the Effect of Indiplon on Sleep Maintenance

Daniele Ouellet, Ph.D. [1], Raymond Miller, D.Sc. [1], Philip B. Chappell, M.D. [2], Robert Farber, Ph.D. [3], Brian W. Corrigan, Ph.D. [1]

[1]Pfizer, Inc., Ann Arbor, MI, [2]Pfizer, Inc., Groton, CT, [3]Neurocrine Biosciences, Inc, San Diego, CA

Background: Indiplon, a new generation $GABA_A$ potentiator, is in development for the treatment of insomnia using two formulations, immediate release (IR) capsules and modified release (MR) tablets, the latter targeting patients with more severe sleep maintenance difficulties. This dose-response analysis was conducted to describe the effect of indiplon on subjective total sleep time (sTST), to determine the impact of covariates, and to assess the time course of response.

Methods: Data were pooled from four crossover Phase 2 studies and five parallel Phase 3 studies, with daily data measured up to 3 months. Indiplon was given at doses of 5 to 40 mg. Dose-response was modeled using a nonlinear mixed effects model. Assessment of the model was conducted by comparing simulated values of the results of another Phase 3 study (N=100 simulations) to the observed data.

Results: A total of 2492 patients were included (109,991 observations), with a mean age of 54 years and 63% women. Baseline sTST values were dependent on gender (women having less severe insomnia), study population (studies using MR tablets having more severe insomnia), and age (elderly having more severe insomnia). Indiplon increased sTST with a maximum response of 386 min, and 50% of the increase observed at a dose (ED50) of 7.8 mg. Response was larger in women (43%) and reduced in elderly patients (13.7%). Response in sleep lab tests was reduced (31.5%) relative to outpatient studies. The efficacy of indiplon was observed following the first dose and was sustained over time. Observed mean sTST from the independent Phase 3 study were within the confidence intervals of the 100 simulated trials.

Conclusions: The dose-response relationship of indiplon for sTST was characterized in insomnia patients, suggesting that doses of 5-15 mg would be optimal. Increased benefit is observed at doses higher than 10 mg. Elderly differ in both disease severity and sensitivity, and a lower dose may be required in this population.

Session II - 104

Eszopiclone Co-Administered with Fluoxetine for Insomnia Co-Existing with Major Depressive Disorder (MDD): Analysis by Severity of Depression

Maurizio Fava, M.D. [1], W. Vaughn McCall, M.D. [2], Andrew Krystal, M.D. [3], Robert Rubens, M.D. [4], Thomas Wessel, Ph.D., M.D. [4], Judy Caron, Ph.D. [4], David Amato, Ph.D. [4], Thomas Roth, Ph.D. [5]

[1]Massachusetts General Hospital, Boston, [2]Wake Forest University, Winston-Salem, NC, [3]Duke University Medical Center, Durham, NC, [4]Sepracor, Inc., Marlborough, MA, [5]Henry Ford Sleep Center, Detroit, MI

Background: Initiation of eszopiclone/fluoxetine co-therapy produced greater improvements in sleep and depression compared with fluoxetine monotherapy in an insomnia and depression study. This analysis was conducted to determine whether baseline depression severity influenced depression and sleep response.

Methods: Patients (n=545) met DSM-IV criteria for major depressive disorder (MDD) and insomnia, received fluoxetine QAMx10 weeks, and were randomly assigned to double-blind eszopiclone 3mg (co-therapy) or placebo (mono-therapy) QHSx8 weeks. Changes in sleep and depression were evaluated within subgroups according to baseline depression severity (less severe=HAMD17 score $\leq$ 22; more severe=HAMD17 score >22).

Results: Median baseline patient-reported sleep measures were worse in the more severely depressed subgroup compared with the less severe subgroup, and mean HAMD17 scores were 26 and 19 for the subgroups, respectively. There were significant changes from baseline measures between treatment groups (co-therapy vs mono-therapy) in both depression subgroups for sleep latency (SL), wake after sleep onset (WASO), and total sleep time (TST) ($p<0.05$). Greater improvements in change from baseline WASO and TST were seen in the more severe subgroup in both treatment cohorts. Significant improvements from baseline ($p<0.05$) were observed with co-therapy at Week 8 in the more severely depressed subgroup for HAMD17 total score (-17 vs. -14 with monotherapy), as well as the following seven individual items: "insomnia" (early, middle, and late), "agitation" and core depression items of "depressed mood," "feelings of guilt," and "work and activities." In the less severe subgroup, the change in HAMD17 total score was greater with co-therapy (-12 vs. -10 with monotherapy; $p=0.1152$), and "insomnia early" was significantly improved relative to monotherapy ($p=0.0012$). Additionally, mean percent changes from baseline in total HAMD17 scores were significantly improved with co-therapy in the more severe subgroup relative to monotherapy (61% vs. 49%, $p=0.0014$).

Conclusions: Eszopiclone/fluoxetine co-therapy resulted in significant improvements relative to fluoxetine monotherapy in sleep measures regardless of baseline depression severity. Additionally, decreases in HAMD17 total scores were observed with co-therapy in both severity subgroups with significant improvements in seven individual items, including three core depression items in the more severely depressed subgroup ($p<0.05$).

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Session II - 94   This poster was not presented at the meeting.

Session II - 95   **Are Changes in Functional Outcomes Associated with Changes in Negative Symptom Factor Scores?**
George Haig, Pfizer Global Research and Development
Dawn Velligan, Mei Wang, Scott Lancaster, Thomas Taylor, Larry Alphs

Session II - 96   **Mapping the Neurocognitive Deficit-Functional Disability Relationship Using Partially Ordered Classification Models**
Judith Jaeger, Zucker Hillside Hospital
Curtis Tatsuoka, Stefanie Berns, Ferenc Varadi, Sarah Uzelac

Session II - 97   **Sedative Effects of Transmucosal Zolpidem**
David Mayleben, Community Research
Bruce C. Corser, Adam Roth, Nikhilesh Singh, Thomas Roth

Session II - 98   **Evaluation of Indiplon Pharmacokinetics and Drug-Drug Interactions**
Brian W. Corrigan, Pfizer Global Research and Development
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Session II - 99   **Efficacy and Safety of Doxepin at 1 mg, 3 mg, and 6 mg Doses in Elderly Adults with Primary Insomnia**
Thomas Roth, Henry Ford Sleep Disorders Center
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Session II - 100   **Sleep Laboratory Assessment of Indiplon in Primary Insomnia: Results of a Double-Blind, Placebo-Controlled, Crossover Trial**
Brian Klee, Pfizer, Inc.
Russell Rosenberg, Yin Kean, Robert Farber

Session II - 101   **Symptom Response and Remission in Insomnia: Analysis of How Various Criteria Perform**
Joanne Bell, Neurocrine Biosciences, Inc.
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Session II - 102   **Paliperidone Extended-Release 3 mg, 9 mg, and 15 mg Tablets: An International 6-Week Placebo-Controlled Trial in Schizophrenia**
Michael Davidson, Tel Aviv University
Robin Emsley, Michelle Kramer, Lisa Ford, Christiana Gassmann-Mayer, Pilar Lim, Guohua Pan, Marielle Eerdekens

Session II - 103   **Dose-Response Analysis of the Effect of Indiplon on Sleep Maintenance**
Daniele Ouellet, Pfizer, Inc.
Raymond Miller, Philip B. Chappell, Robert Farber, Brian W. Corrigan

Session II - 104   **Eszopiclone Co-Administered with Fluoxetine for Insomnia Co-Existing with Major Depressive Disorder (MDD): Analysis by Severity of Depression**
Maurizio Fava, Massachusetts General Hospital
W. Vaughn McCall, Andrew Krystal, Robert Rubens, Thomas Wessel, Judy Caron, David Amato, Thomas Roth

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